Research on drug abuse abstracts
1975/76

RESEARCH ON DRUG ABUSE ABSTRACTS 1975/76
RÉSUMÉS DE RECHERCHE SUR L'ABUS DES DROGUES 1975/76

Health and Welfare Canada
Santé et Bien-être social Canada

RESEARCH ON DRUG ABUSE
ABSTRACTS 1975/76

PROJECT OF THE NON-MEDICAL

USE OF DRUGS DIRECTORATE

RÉSUMÉS DE RECHERCHE SUR L'ABUS
DES DROGUES 1975/76

PROJET DE LA DIRECTION DE L'USAGE

NON MÉDICAL DES DROGUES

Published by authority of
the Honourable Marc Lalonde
Minister of National Health
and Welfare

Publication autorisée par
l'honorable Marc Lalonde
Ministre de la Santé nationale et du
Bien-être social

INTRODUCTION TO RODA ABSTRACTS

The Non-Medical Use of Drugs Directorate supports research directed toward providing information about all facets of drug abuse. The Directorate often receives requests from interested persons in the scientific community for detailed information concerning the research being supported. In response to these requests the Directorate makes available abstracts of all funded research projects.

The abstracts contained in this booklet are of a highly scientific and technical nature and are therefore published in the language of the authors. No attempt has been made by the Directorate to edit or evaluate this material and the abstracts are reproduced directly from the form that was sent to the researchers. All abstracts received in Ottawa by the deadline date are presented in the booklet. It is regrettable that some researchers were unable to submit their abstracts in time for inclusion. The appendix contains the names of all researchers we are funding.

For the convenience of readers, the abstracts in this book have been divided into five categories. These categories are evaluation, biomedical, behavioural, social science and multi-disciplinary. Within each category, projects are presented according to the alphabetical order of the surname of the principal investigators.

It is with pleasure that the Non-Medical Use of Drugs Directorate presents to you this booklet of abstracts.

INTRODUCTION AUX RÉSUMÉ DE PROJETS DU PROGRAMME DE RECHERCHE SUR L'ABUS DES DROGUES

La Direction de l'usage non médical des drogues subventionne de l'abus des drogues. La Direction reçoit souvent des demandes de renseignements de personnes intéressées, du domaine scientifique, sur la recherche subventionnée. Pour répondre à ces demandes la Direction présente les résumés de projets de recherche subventionnés.

Les résumés présentés dans cette brochure sont de nature scientifique et technique et paraissent donc dans la langue de l'auteur. La Direction n'a ni révisé ni évalué ces ouvrages et a reproduit les textes directement du formulaire envoyé aux chercheurs. Tous les résumés reçus à Ottawa avant la date limite sont présentés dans cette publication. Il est regrettable que certains aient été reçus trop tard pour y être insérés. Les noms de tous les boursiers figurent en appendice.

Pour faciliter la consultation, les résumés sont divisés en cinq catégories: évaluation, recherche biomédicale, recherche sur le comportement, sciences sociales et recherche multidisciplinaire. Au sein de chaque catégorie, les projets sont classés selon l'ordre alphabétique des noms des principaux chercheurs.

C'est avec plaisir que la Direction de l'usage non médical des drogues vous présente cette brochure de résumés.

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MULTI-DISCIPLINARY
MULTI-DISCIPLINAIRE

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
B.K. Alexander	PSYCHOLOGY
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
SIMON FRASER UNIV. – BURNABY, B.C.	
PROJECT TITLE – TITRE DU PROJET	
INTERPERSONAL PERCEPTION IN FAMILIES OF HEROIN ADDICTS	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
74–75	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE 291–3743

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☑ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

B.K. Alexander & G.S. Dibb

Interpersonal Perception in Families of Heroin Addicts

Q-sort data were used to make inferences about interpersonal perception in families of heroin addicts and matched controls.

The utility of such an analysis arises from relatively new conceptualizations of addiction of psychopathology. First, less importance is being accorded to dependence as a cause of addiction. Numerous lines of evidence suggest that aids to withdrawal from physical dependence are relatively ineffective in the treatment of addictions. Instead the addict needs to be helped to develop a satisfying alternative to the degraded life style in which opiate use is irresistible (e.g., Khantzian et al., 1974).

Second, psychopathology is being more and more related to the social pressures arising from the family. Symptoms of one family member may serve to keep the rest of the family together (Haley, 1973) or may reflect habitual inconsistency in communication patterns and affect (Bateson et al., 1956).

We have identified a subgroup of heroin addicts in Vancouver (about 25% of the addict population) who maintain close ties with their parents. We have proposed that the nature of these "addict-families" may be crucial in whether or not addicts succeed in developing a viable alternative to their life as heroin addicts (Alexander & Dibb, 1975). In the present paper we compare patterns of interpersonal perception as reflected in correlations between Q-sort descriptions of themselves and the others by family members in addict families and control families which no member of the family is addicted. In comparing 66 mean correlations between the experimental and control groups 20 significant differences were found. The pattern of differences suggested the following generalizations:

(1) Relative to offspring in control families, addicts were described, both by themselves and their parents, as highly discrepant from their own ideals.

(2) Descriptions of the offsprings' ideal were very similar whether they came from offspring or parents, addict families or control families.

(3) Relative to offspring in control families, addicts were described as dissimilar to both of their parents, regardless of who in the family made the description.

(4) Relative to control families, parents and offspring in addict-families agree less in their description of the addict.

(5) Addicts and their parents both indicate discrepancies between the addict and his ideal which when taken together suggest passivity and dependence. However there are also some glaring discrepancies in the self-ideal discrepancies perceived by parents and addicts.

(6) Offspring in both addict and control families describe their parents as fairly similar to the offspring's ideal.

(7) Relative to control families, mothers in addict families describe themselves in terms which are more discrepant from the generalized ideal.

We discussed these differences in terms of their effect on the addicts self-perception and his likelihood of achieving the independence and self-sufficiency which could make life without heroin feasible. We also discussed the results in terms of the desirability of family therapy as a mode of intervention.

References

Alexander, B.K. & Dibb, G.S. Opiate addicts and their parents. Family Process, 1975, 14, 499-514.

Bateson, G., Jackson, D.D., Haley, J., & Weakland, J.H. Toward a theory of schizophrenia. Behavioural Science, 1956, 1, 251-264.

Haley, J. Uncommon therapy: The psychiatric techniques of Milton H. Erickson, M.D., N.Y.: Ballantine Books, 1973.

Khantzian, E.J., Mack, J.F., & Schatzberg, A.F. Heroin use as an attempt to cope: Clinical observations. American Journal of Psychiatry, 1974, 131, 160-164.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
J. Allan Best, Ph.D.	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B.C. V6T 1W5

PROJECT TITLE – TITRE DU PROJET
Smoking Withdrawal Procedures Tailored to Individual Reasons for Smoking

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
September 1974-August 1976	$50,507.40	604-228-4622

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[ ] BIOMEDICAL – BIOMÉDICALE
[X] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Project Description

The project has two major objectives. The first stems from the problem of extensive relapse subsequent to initial success in smoking and drug withdrawal. In an effort to improve maintenance of behaviour change, treatment procedures assess the instrumental or functional utility of an individual's smoking, identify or train appropriate functional alternatives, and in addition train general self-management skills.

The second objective is to incorporate dissemination into the development of the treatment package. Procedures are designed to be straight-forward and well standardized and to involve a minimum of professional time and no special equipment. Programme issues and methods of dissemination will be evaluated as the treatment package is offered through existing public health and preventive medical services.

Key Findings

The programme currently involves five treatment sessions and can be successfully administered with as little as ten hours of training. Initial success levels for the first 60 subjects were high and good maintenance at a six month followup was typical. No significant differences were found in the relative effectiveness of variations in aversive, oversmoking procedures. Results were taken to indicate (a) the feasibility of a self-managed treatment programme amenable to public health utilization and (b) a sufficient level of success and maintenance to warrent packaging and dissemination. More broadly, the data support the utility of planning specific coping strategies and identifying functional alternatives for the instrumental objectives of drug use.

Future Directions of Research

Current studies include:

(a) the factor analytic development of a situational model of reasons for smoking
(b) evaluation of the role of systematic recording of reasons, planning for alternatives, and written instructions on treatment outcome
(c) evaluation of the effects of group size and phone support on treatment efficacy.
(d) a feasibility study for administration of the programme by volunteers in a public health clinic.

Future studies will be primarily concerned with dissemination, evaluating treatment outcome as a function of training techniques, treatment setting, therapist background, etc.

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NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Walter D. Fenz, Ph.D.	Psychology
INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE	
University of Waterloo, Waterloo, Ontario N2L 3G1	
PROJECT TITLE - TITRE DU PROJET	Psychophysiological Reactions to Cannabis Sativa in Chronic Users
YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☒ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

A series of experiments have recently been completed in our laboratory on the Psychophysiological effects of marihuana on chronic male users. In a first study we replicated Lacey's (1950) methodology, and established individual response hierarchies for 15 Ss under various conditions of physical and mental stress. Dependent variables included measures of electrodermal cardiovascular, striated muscle, and respiratory activity. The same Ss were re-tested under the same physical and mental stress conditions, after having smoked 1.15 g of marihuana (1.1% Delta-THC). A disruption of individual response hierarchies was noted, with an emphasis of responding in the cardiovascular system.

A second experiment included 3 groups of 15 Ss each, receiving low (.66 g), medium (1.15 g) and high (1.64 g) doses of marihuana, as well as a control group of chronic users, who were given no drug. Testing followed a modified, aversive cardiac conditioning paradigm. Conditioning, as measured through a number of indicants, was inversely related to amount of marihuana smoked. The data were analyzed both in terms of the cardiac activity, as well as in terms of other physiological measures which are known to act as mediators of the cardiac response.

Finally, subjective ratings of anxiety were obtained throughout a two-hour period after intake of 1.15 g of marihuana, as well as measures of physiological arousal. The findings indicated a clear dissonance between the subjective experience of marihuana intoxication and the physiological, objective state of the organism.

Reference

Lacey, J.I. Individual differences in somatic response patterns. J. comp. physiol. Psychol. 1950, 43, 338-350

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
R.M. Gilbert	Research

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Addiction Research Foundation, 33 Russell Street, Toronto, M5S 2S1

PROJECT TITLE — TITRE DU PROJET
Temporal and volitional factors in the development and assessment of physical dependence on ethanol in rats.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975-76, 1976-77 (part of each)	$16,804	(416) 595-6169

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
[ ] EVALUATION — ÉVALUATION
[X] BIOMEDICAL — BIOMÉDICALE
[X] BEHAVIORAL — COMPORTEMENT
[ ] SOCIAL SCIENCE — SCIENCES SOCIALES
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1. Description of Project

The primary concern is with the role of degree of dose division in the development of physical dependence on ethanol. More specifically - does the severity of dependence resulting from chronic administration of a given daily dose of ethanol vary with the frequency of division of the dose? For example, are withdrawal symptoms more severe if 8 g/kg is given in one daily dose or in four 2 g/kg portions every 6 hours?

The secondary concern is with the role of 'voluntary' consumption of ethanol. Does the severity of physical dependence vary according to whether the ethanol is drunk by the animal or forcibly administered, and to whether withdrawal is precipated by removing ethanol or by providing a more palatable fluid.

Ethanol drinking sufficient to cause physical dependence is induced by spaced feeding of small portions of the food ration (schedule induction). Ethanol is otherwise administered by gastric tube.

Recorded signs of withdrawal include general hyperactivity, spontaneous tremors, and spontaneous and sound-induced seizures.

Notification of the award was made in October 1975. Preliminary experimental work began in November 1975. Sufficient funds are available for work until July 1976. The proposed duration of the project was 21 months.

2. Key Findings

One experiment has been completed. Ethanol administered by gastric tube was found to produce more severe withdrawl signs when 8 g/kg/day was given in 4 equal doses administered 45 minutes apart than when the same daily amount was given in 4 equal doses administered 6 hours apart. Thus, contrary to the general direction of the literature, greater division of a given daily ethanol dose appears to reduce the severity of subsequent withdrawal signs. Rats receiving 4 administration of 2 g/kg at 45 minute intervals did not maintain good health, unlike rats who received greater division of the same total daily dose. The apparent severity of withdrawal signs could have been more closely related to degree of debilitation caused by extreme intoxication than to other aspects of the differences in division of doses.

The second experiment is underway. A preliminary finding is that rats drink more ethanol solution when each day contains six 1-hour schedule induction periods than when each day contains one 6-hour period. Water drinking, by contrast, does not show the same difference, suggesting an effect of ethanol on schedule-induced drinking of ethanol.

3. Significance of Project

The work will help clarify the respective roles of average and peak blood levels in the development of physical dependence on ethanol. Such clarity would, in conjunction with other knowledge of the pharmacokinetics and pharmacodynamics of ethanol, allow greater understanding of the mechanism of ethanol's action on the nervous system and hence the pharmacological basis of ethanol dependence.

Significant differences in severity of withdrawal following forced- and self-administration of similar doses of ethanol on similar schedules would suggest a hitherto-unreported role of drug-using behaviour in physical dependence.

4. Relevance

Inasmuch as physical dependence is a determinant of non-medical drug use, further understanding of the mechanism of physical dependence is likely to be of considerable value in reducing such drug use and/or its associated problems. The project may also help elucidate the role of drinking per se in alcohol use, thus allowing determination of the extent to which alcohol abuse is a drinking problem rather than a drug-use problem.

5. Future Directions

Because work has just begun, and because future work will be determined to a large extent by what happens during the present series of experiments, indication of future directions may not be helpful at this stage, expect to say that the roles of dose division and of self-administration are of interest with respect to many drugs other than ethanol, including opiates and barbiturates. The project could be expanded to include consideration of these classes of drug.

February 12, 1976

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
YVES LAMONTAGNE, M.D.	SERVICE DE RECHERCHE, INRS-Santé

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Hôpital St-Jean de Dieu, Montréal, H1N 1Z0, Qué.

PROJECT TITLE TITRE DU PROJET Etude comparée de l'arrêt des pensées, du contrat behavioral et de la combinaison des deux techniques sur le comportement des fumeurs.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-76	$13,467.00	253-2832

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
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[X] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

La présente étude se veut une continuation de l'expérience précédente "The thought-stopping technique as a treatment for reducing cigarette smoking". Nous voulons, dans le projet actuel, augmenter encore davantage l'efficacité thérapeutique. Nous croyons que pour être encore plus efficace, le traitement devrait s'étendre sur une plus longue période de temps et que la technique de l'arrêt des pensées devrait être combinée à une autre méthode pour augmenter l'efficacité thérapeutique. Enfin, il faudrait trouver un moyen pour que les sujets puissent facilement continuer à pratiquer la technique à la maison, en dehors des séances de thérapie. La présente recherche tend vers ces buts.

Cent vingt sujets ont participé à l'expérience qui a duré douze semaines au lieu de 4 semaines, comme dans l'expérience précédente et ont été divisés au hasard en 4 groupes de 30 sujets.

1) Arrêt des pensées: la pratique a domicile a été rendue plus facile au moyen d'une cassette pré-enregistrée qui a été distribuée à chaque sujet de ce groupe.

2) Le contrat behavioral: une technique d'auto-contrôle.

3) Combinaison des deux techniques: arrêt des pensées et contrat behavioral.

4) Groupe témoin: non traité pour évaluer les variables extra-thérapeutiques.

La technique d'auto-contrôle (contrat behavioral) vise le contrôle externe, i.e. le contrôle du stimulus et la technique de l'arrêt des pensées met l'accent sur le contrôle interne (éliminations des ruminations en rapport avec le goût de fumer). Ces deux procédures ne sont pas mutuellement exclusives et leur combinaison ne devrait qu'augmenter les chances de succès.

L'expérience est complètement terminée. Nous en sommes maintenant à faire les analyses statistiques requises avant de passer à la rédaction de cette expérience.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
YVES LAMONTAGNE, M.D.	SERVICE DE RECHERCHE, INRS-Santé
INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE	
Hôpital St-Jean de Dieu, Montréal, H1N 1Z0, Qué.	
PROJECT TITLE - TITRE DU PROJET Rôle de la rétroaction biologique (Biofeedback) par EEG et EMG dans la prévention de l'abus des drogues.	
YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES
1974-75 et 1975-76	$49,189.70 et $27,205.50

TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE: 253-2832

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMEDICALE [X] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

A la suite des résultats obtenus avec nos 24 premiers sujets [1], nous avons continué l'expérience avec intérêt. Notre but est d'examiner les changements dans la consommation des drogues chez 75 volontaires en comparant un groupe d'entraînement à l'alpha feedback et en groupe d'entraînement à l'EMG feedback, à trois autres groupes soumis respectivement à une simple consigne de relaxation, à une pseudo-rétroaction et à aucun traitement.

Pour éviter les biais, plusieurs mesures sont utilisées: standardisation des conditions expérimentales (techniques, mesures, influence des expérimentateurs, directives); contrôle des défections, de la contagion et des facteurs temporels . En plus des mesures physiologiques (EEG, EMG, ECG), des questionnaires sur la consommation de drogues, l'anxiété, le sommeil et les résultats scolaires, sont utilisés avant, pendant et après l'expérience (1, 3 et 6 mois). L'expérience est maintenant terminée et nous sommes à l'analyse des résultats.

Les résultats permettront d'évaluer et de comparer l'efficacité respective de deux types de rétroaction biologique pour

1) empêcher le développement d'une toxicomanie établie chez des jeunes qui prennent de la drogue,

2) trouver une nouvelle forme de traitement rapide, et efficace, comme solution de rechange à la toxicomanie,

3) apprécier leurs effets possibles sur l'anxiété, le sommeil et les résultats scolaires.

Si les résultats sont satisfaisants quant à la consommation des drogues et autres variables étudiées, en plus de la nouveauté, de la rapidité et de l'efficacité de ce mode de traitement, les autres avantages peuvent principalement s'énumérer en fonction de la possibilité de traitement en groupe, de même que du traitement combiné (i.e., rétroaction biologique et autres formes de traitement) pour augmenter encore plus les chances de succès thérapeutiques chez les toxicomanes.

1) LAMONTAGNE Y., HAND I., ANNABLE L., & GAGNON M.-A.: Physiological and psychological effects of alpha and EMG feedback training with college drug users: a pilot study. Can. Psychiat. Assoc. J., 20: 337-349, 1975.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
W. A. W. MacLean	Psychology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Queen's University, Kingston, Ontario	
PROJECT TITLE – TITRE DU PROJET	
Responding During Sleep: A Paradigm for Drug Evaluation	

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
August 1973 - July 1976	$68,979.00	613-547-2697

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMÉDICALE [X] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Description

The aim of this study was to establish dose-response relationships between moderate doses of ethanol and human sleep.

Ten, young, adult male subjects were seen in a balanced latin square design. Following one adaptation night, Ss were seen on five occasions with five nights intervening between each night. Following baseline testing, they consumed a beverage containing either 0.00, 0.25, 0.50, 0.75 and 1.00 gm./kg. body weight of absolute ethyl alcohol (USP) together with 4 ml. of tincture of gentian and made up to a total of 500 ml. with fresh orange juice. They were then tested by means of a breathalyser, a body sway test and subjective ratings as soon as they consumed the alcohol, 20 minutes later and 40 minutes later. They then went to bed having had electrodes attached for standard sleep recordings (Rechtschaffen and Kales, 1968). In the morning they were again tested.

On the basis of the previous literature it was predicted that (1) Rapid Eye Movement (REM) sleep would be suppressed, (2) Stage 3 + 4 would be enhanced and (3) these changes would be dose dependent.

Key Findings

The alcohol doses produced mean blood alcohol values of 0.000, 0.008, 0.030, 0.049 and 0.074 respectively. There was a significant increase in body sway with increasing dose immediately following alcohol ingestion but this was not apparent on the next morning. There was a significant increase in the degree of subjective discomfort (hangover) with increasing dose levels.

The results demonstrated no statistically significant support for the first prediction but supported the second and third predictions. Over the whole night there were no statistically significant differences in either REM or SW sleep. However, in the first three hours of sleep there were significant increases in SW sleep. In general, a dose-dependent relationship was apparent even when no statistically significant differences were found.

Significance

The results are interpreted as (1) providing support for the position of Gross et al. (1971) regarding the important of REM and SW sleep in understanding the effects of alcohol in patient and non-patient groups and (2) the possible existence of individual differences in response to alcohol ingestion (3) subjects showed consistently increased REM time following alcohol.

Relevance

Sleep disturbance has been implicated as both a causal agent and a correlate of alcoholism. Sleep recordings provide an elegant, sensitive and relevant technique for the investigation and description of the human response to alcohol.

Future Directions

Knowledge of the sleep cycle response to alcohol must be extended across the entire range of drinking experience from the novice drinker to the chronic alcoholic. There is every reason to believe that by doing this it will be possible to develop an objective, and sensitive measure of the individual's tolerance for and potential risk in relation to alcohol.

Publication

These findings were presented to the 14th Annual Meeting of the Association for the Psychophysiological Study of Sleep in Jackson Hole, Wyoming, 1974. (MacLean and Cairns, 1974).

References

Gross, M.M. et al. Sleep Disturbances in Alcoholic Intoxication and Withdrawal. In Recent Advances in Studies of Alcoholism, NIMH, 1971.

MacLean, A.W. and Cairns, J. Dose-response relationships between ethanol and human sleep. Sleep Research, 1974, 3, 59.

Rechtschaffen, A. and Kales, A. (Eds.) A manual of standardized terminology techniques and scoring system stages of human subjects. 1968.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
H.B.M.Murphy	Psychiatry
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
McGill University, Montreal, Quebec.	
PROJECT TITLE – TITRE DU PROJET	
Hidden Barriers to the Diagnosis and Treatment of Alcoholism.	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
1975-76	$ 17,770

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE: 392-5164

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION – ÉVALUATION ☐ BIOMEDICAL – BIOMEDICALE ☑ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Evaluation studies have shown that only one alcohol-abuser in ten or in twenty is under treatment in a given year, and that most of those that come into treatment do not stay long. Quite a number of explanations for this well-known fact exist, but it is impossible at the present time to know what weight to give them, and several appear too superficial. Surveys have repeatedly shown that therapists of all kinds feel uncomfortable with the alcoholic, and this discomfort does not seem adequately explained by the fact that good results are uncommon, or because the alcoholic's "weakness of willpower" is disapproved of, or because the patients sometimes arrive drunk and do not pay their bills. There would appear to be hidden or unrecognised barriers to the diagnosis and treatment of alcohol abuse, and the purpose of the present research was to see whether these could be uncovered.

The method involves three different levels of approach, with both the physician's and the patient's point of view being sought at each level. Most superficially, questionnaire cards are being employed in general practice and general clinic waiting-rooms, with a view to seeing (a) whether patients who admit through the questionnaire to having a drinking problem have ever mentioned this to their doctor; (b) whether the doctor has been independently aware of this problem; (c) the action which the doctor thinks appropriate; and (d) what the patient understood the doctor to have recommended. At the second level, interviews are being carried out with various categories of physician and of current or former alcohol-abusers, with a view to getting each party's description of the interaction that takes place when a patient reveals, intentionally or otherwise, that he has a drinking problem. At the third level, psychoanalysts are being asked to describe alcohol-abusing patients that they have recently treated, and to discuss the psychodynamics which these patients exhibited, while a few former alcohol-abusers who had been in analytic treatment have also been asked to describe what they felt their analyst to have done about the problem.

The professionals were located through lists of medical society members, through contacts in four hospitals, and among our acquaintances, but care was taken to avoid interviewing anyone who specialised in the treatment of alcoholism since it was thought that their attitudes on this subject would be unrepresentative. The patients and ex-patients were located through A.A., through a mental hospital, and through a general hospital alcoholism clinic. The patients and ex-patients were asked not about their current therapy but about earlier contacts that they had had with doctors on occasions when a drinking problem had been mentioned or had been so obvious that the physician ought to have noticed it.

At time of writing, the data from the first level have not yet been examined, but tentative conclusions from the other two levels can be offered. These conclusions are as follows:

1. Most alcohol-abusers who go to a physician for any reason are likely to respond fairly honestly when correctly questioned regarding their drinking habits, unless the physician is seen as in a position of authority, e.g. as representing an employer, in which case denial is the commoner attitude even when confidentiality is promised.

2. If physicians do represent an external authority they do usually ask about drinking and seem to feel no discomfort at this, but most other physicians, including psychiatrists and psychoanalysts, do not pose the necessary questions. Moreover, a substantial percentage of them appear to evade the issue when a patient expresses the fear that he may become an alcoholic.

3. The major reason why physicians (and other types of therapist) tend to evade the matter is that they feel they have no effective medical treatment to offer. Most industrial medical officers do not share this feeling of impotence, since they see quite a number of cures, but a closer consideration of the way in which the cure has been brought about shows that it is through the employer's coercive powers and not usually thanks to any medical act.

4. The feeling of impotence which most non-industrial physicians communicated is apparently rooted in the lack of training for the task, and nearly everyone thought that such training ought to be improved. However, an additional reason is probably the feeling that most of the patients could cure themselves without medical aid if they only wished to, a feeling which is strengthened by the fact that A.A.'s non-medical approach appears as successful as any medical one.

5. The current model of the physician as someone who in theory leaves the important decisions to the individual patient and is responsible only to his patients, not to society, also hampers therapy, insofar as the alcoholic's inability to decide to his best advantage is not allowed for in this model.

6. Alcohol problems are relatively common in the family histories of physicians (e.g. in a parent, spouse or their own college years) and the way in which these problems have been handled may help to determine how similar problems in their patients will be handled. If they have been confronted and mastered or seriously worked with, there is likely to be little difficulty in handling evidence of alcohol abuse in a patient.

The relevance of these conclusions, if they are confirmed on closer examination, is obvious. Conventional methods of training medical students with respect to alcoholism do not face up to the real problem, and it seems as though a much more subtle and complex approach is going to be necessary, one which involves a re-examination of the physician's role and the means which he has of helping people. Mastery of medical knowledge, which is so important with other diseases and which gives many physicians their main satisfaction, seems much less important here than discreetly cooperating in a general social effort to enable the patient to gain mastery over himself; and this more modest role is not one which medical schools are teaching.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Bruce A. Pappas	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Carleton University, Colonel By Drive, Ottawa, Ontario

PROJECT TITLE - TITRE DU PROJET

An exploratory investigation of Pavlovian mechanisms in morphine tolerance

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
October 1975 - March 1977	$21,975	231-3638

FIELD OF RESEARCH SUJET DE LA RECHERCHE

EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
☐	☒	☒	☐	☒

The possibility that drug-predicting stimuli would elicit drug-like responses was indicated about 60 years ago by Pavlov. While current medical practice recognizes this phenomena by its utilization of the placebo, remarkably little research has been directed at determining the laws governing it. Indeed, these stimuli have also been shown to elicit responses opposite to those produced by the drug. The purpose of this project is to determine whether the presence or absence of a predicting stimulus alters the actual responses to the drug in the rat and secondly, whether this stimulus elicits drug-like or the opposite placebo response. The research, which has been underway for about 5 months is currently focused along two dimensions.

First, we are determining whether the analgesic (hot plate) effect of morphine is effected by morphine predicting stimuli. Rats have received 4 morphine injections on alternate days, with the injections always signalled by a unique stimulus complex. Placebo administrations on intervening days are signalled by a different stimulus. On the test day, the rats receive either morphine or placebo, preceded either by the morphine or placebo predicting stimulus and tested for thermal pain sensitivity. The results of one completed experiment indicate that rats who expect morphine because the morphine predicting stimulus was presented, but who actually receive placebo, were hyperesponsive to painful heat. Thus this stimulus seems to elicit an anticipatory response counteractive to the actual drug effect. However, morphine analgesia itself was unaffected by the stimulus. Furthermore, while anticipation elicited behavioral compensation, no anticipatory change was observed in body temperature suggesting a dissociation between the overt behavioral and the covert physiological preparation. Currently, we are replicating this experiment and in addition, determining whether the magnitude of the behavioral response is related to the drug dosage - our prediction is that the greater the drug effect, the more intense the anticipatory behavioral compensation.

In the second phase of our research, we administer morphine intravenously to rats who are maintained chronically in isolation chambers. We continuously record the deep core temperature by means of implanted thermistors and the cardiac response to morphine in rats who receive the drug unsignalled or preceded by a signal. At the termination of the experiment, the rats receive only the signal and a placebo. This research is only in the early instrumentation stage. However, we have developed what appears to be a significant new technique for chronic intravenous drug infusions utilizing a combination electrode connector-fluid feedthrough which is permanently implanted on the rats skull and connected to a swivel arrangement. This system has several advantages, including a minimum restraint of the animal and the capacity to transmit at least 6 channels of biopotential data while simultaneously infusing drug.

We expect that our findings will not only permit a more rational interpretation of the role of conditioning in modulation of drug responses but might also suggest how environmental stimuli ought to be manipulated so as to control drug related motivation. To this end, our future research will concentrate on the control of drug self administration by stimuli predictive of the impending presence or absence of morphine. Finally, we anticipate determining to what extent the lethality of drugs is dependent upon these stimuli.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
R.O. Pihl	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
McGill University, Montreal, Quebec, Canada H3C 3G1

PROJECT TITLE – TITRE DU PROJET
Extra-Pharmacological Factors in Drug Intoxication

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-77	$55,965.00	392-4702

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
☐ EVALUATION – ÉVALUATION ☐ BIOMEDICAL – BIOMEDICALE ☒ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Previous research has indicated that situtation specific environmental variables may significantly determine the effects of smoking marihuana. Four studies currently underway and two recently completed represent attempts to delineate, understand, and manipulate these extra-pharmacological variables.

Studies I and II were designed to assess the feasibility of interfering with marihuana intoxicated high by the presentation of aversive stimuli. We were interested in determining the differential effects of marihuana when used in an environment which is judged pleasant and one which is judged unpleasant, i.e., aversive. Briefly, marihuana-experienced males were randomly assigned to a high dose, low dose, placebo or coltsfoot (control) drug condition. Ss rated themselves before and after each session on the Clyde Mood Scale and throughout each session on the "How High Scale," "How Relaxed Scale," and "Environment Rating Scale." Pulse rate was monitored throughout each session and blood pressure was taken before and after each session. In Study I music plus a high pitched disruptive auditory stimulus was presented to Ss at specific times during the experimental smoking session, whereas only music was presented in the control session. A one way times series ANOVA yielded numerous significant results. Clearly, the presentation of noise was aversive for all groups, disrupted marihuana intoxication seemingly more so for the low dose than high dose condition, and had a more pronounced effect on subjective ratings of relaxation and the environment than on ratings of intoxication and pulse rate.

There is evidence that subjective aversiveness is mediated by a unitary mechanism common to all sensory modalities, i.e., noxious stimuli of all types share a common aversiveness continuum (Woods and Campbell, 1967; Sullivan and Shenker, 1971). With that in mind, Study II was a replication of Study I, the presence or absence of an odorous substance being the aversive stimulus. Two placebo cigarettes containing finely cut amounts of a non-toxic odorous substance were presented in place of disruptive noise. Results of Study II have yet to be fully analyzed.

A discordance was found between measures of pulse rate and subjective "How High" ratings in Study I. Though all groups rated their "high" as lower as a result of noise, the high dose marihuana group did not display a similar fluctuation in pulse rate. Pulse rate has been found to be a consistent indicator of intoxication (Weil, Zinberg, and Nelson, 1968; Jones and Stone, 1970; Beaconsfield, Ginsberg and Rainsbury, 1972) and appears to be dose-dependent (Hollister, 1971). The same statement can be made for the "How High Scale" (LeDain Commission ...1972; Adamec, 1973). The discrepancy found between these two measures raises questions concerning how the physiological and subjective measures are related to each other, and what the differential contribution of these mechanisms to the "high" are.

Study III is an attempt to clarify the interaction between psychological and physiological aspects of the marihuana "high" by manipulating pulse rate. Pulse rate has been found to be amenable to biofeedback techniques (Wells, 1973; Gutchel, 1974; Blanchard, 1974). This study utilizes biofeedback training to teach subjects to both increase and decrease pulse rate at particular times during smoking sessions. Of most interest will be correlations between sub-

jective ratings of "high" and changes in pulse rate. Drug effect, increase/decrease effects, and drug x increased effects will be analyzed.

As a motivational variable may be involved as a basis for many of these extrapharmacological effects, Study IV is designed to assess this variable. All subjects are randomly assigned to either a drug or no drug condition, and then assigned to one of four motivational conditions. Subsequently the Ss are administered a complex paired associate test, which has been shown by Pihl and Grinspoon (1969) to be quite responsive to subtle changes in reinforcement. In addition a time estimation task and complex reaction time task will be administered to provide information on cognitive and psychomotor performance in intoxicated/straight and motivated/no motivation conditions. Results of this study will be analyzed to assess the effect of motivation on acute intoxication, the effect of differential amounts of motivation, and the possible interaction between dosage and motivation.

Additionally, our concern with the parameters of intoxication has led to the design of two studies attempting to ascertain the characteristics of the intoxicated state and to determine whether non-intoxicated individuals (both marihuana naive and experienced) can recognize these characteristics. In Study V, 20 non-experienced and 20 experienced marihuana smokers rate videotapes of individuals in placebo, coltsfoot, low and high dose conditions for degree of intoxication and characteristic behavior patterns. Study VI is a replication of Study V, the difference being that subjects are taught to recognize factors associated with the intoxicated state prior to rating, whereas in Study V no such cues are given.

We would like to draw attention to the possible therapeutic value in being able to interrupt an intoxicated state, and the potential development of prevention programs utilizing motivational and extrapharmacological factors. These studies would also seem to be paradigmmatic, in that although cannabis has been the drug of concern, questions asked concerning cannabis may also be appropriate to other abused substances.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Sam Revusky	Psychology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Memorial University of Newfoundland, St. John's, Newfoundland

PROJECT TITLE — TITRE DU PROJET
Basic Research Relevant to the Chemical Aversion Treatment of Alcoholism 1975

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
		753-1200 Ext. 3293

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMÉDICALE ☒ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

There have been two findings of importance to the treatment of alcoholism.

In the chemical aversion treatment of alcoholism, patients are made sick by means of a drug or by induction of motion sickness after they consume alcoholic beverages in the hope that this will produce a therapeutic aversion to them. It seemed as though such a method might lose efficacy after a few treatments because rat experiments have shown that repeated administrations of sickness reduce its capacity to produce a flavor aversion; if so, the capacity of sickness to produce therapeutic aversions to the alcohol would be expected to decrease over a series of treatments. However, together with L. Parker, S. Coombes, and J. Coombes, I discovered that repeated exposure to sickness reduces its capacity to produce a flavor aversion only if the sickness is not preceded by ingestion. Otherwise, repeated sickness actually increases the capacity of sickness to produce flavor aversions. This work will appear probably in the June issue of Behavior Research and Therapy. My colleague, Dr. Clive Mellor of the Psychiatry department here, has found a similar effect in human patients; after repeated pairings of alcohol consumption with lithium sickness, the alcohol produces a conditioned lithium sickness which summates with the unconditioned sickness. A cognate finding by Revusky and Parker supported by NRC is that familiarity of a flavored substance does not prevent aversion learning. In this study, to appear in the October issue of the Journal of Experimental Psychology, it was found quite easy to produce aversions to familiar flavored water in rats by means of contingent sickness.

On the basis of common sense, it would seem that a drug state could be made aversive by occurring prior to another, highly aversive drug state. Thus, for instance, a heroin addict, might be treated by pairing heroin state with later sickness. However, we had found earlier that not only does this principle not work, but it produces a counterproductive result. If pentobarbital sedation is paired with lithium sickness in rats, the capacity of pentobarbital sedation to produce a flavor aversion is reduced; according to our original common sense notions, it should have been increased. During the term of the continuation grant, we found that this basic effect also occurs when ethanol or amphetamine is paired with lithium sickness. Oddly enough, after pentobarbital has been paired with consumption of a flavored solution, pairings of pentobarbital with lithium sickness reduce the preference for the flavor; this is the opposite of the result which is obtained when the pairings of pentobarbital with lithium sickness precede the pairings of pentobarbital with a flavored solution. The net result is that we have found theoretical evidence against a class of behavior therapies which are bound eventually to be tried in clinical settings by those unfamiliar with our work. Some of these findings will soon appear in Pharmacology, Biochemistry & Behavior

We had originally proposed some work on making a flavor aversion more specific to alcohol, but this work has already been done successfully by Nicholas Luongo of the University of California at Los Angeles and so there was no necessity to repeat it.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Thomas Stormont R.E. Cutler	Psychology
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	
University of British Columbia, Vancouver, B.C. V6T 1W5	
PROJECT TITLE – TITRE DU PROJET	
Observational Study of Alcohol Consumption in Natural Settings	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
1975-1976	41,418.82
TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE	
228-3008	

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☑ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

There is a complex system of interrelationships among general population consumption of alcohol, frequency and type of drinking occasion, distribution of consumption on single occasions, incidence of alcohol problems related to blood alcohol on a given occasion, problems of alcoholism related to long-term consumption, institutional responses to alcohol problems, and public attitudes to alcohol. Many of the basic descriptive facts essential to a clear understanding of these relationships are only vaguely known. This study is intended to aid in the specification of some of the basic facts, namely the distribution and correlates of alcohol consumption in three common types of drinking occasion, the beer-parlor, the cocktail lounge, and the private party. Much of the consumption of alcohol takes place in these three settings.

Two three-man teams of observers were stationed in four beer parlors and four cocktail lounges in Vancouver, on eight successive week-ends. Observations were made on two nights, Friday and Saturday, in each of these locations from 7 p.m. to 3 a.m. Each team selected a number of tables and unob trusively recorded sex, estimated age, estimated weight, number in party, duration of the occasion, number of drinks per subject, and time interval of each successive drink. The total sample of subjects observed was approximately 600 in beer parlors and 800 in cocktail lounges. These data were obtained from October through December, 1975.

In order to obtain more detailed quantitative data on drinking rate, a second sample of subjects was observed from January through March 1976. The same basic procedure and the same observations were made, with the addition of time of each individual sip. The sample was obtained again in four beer parlors and four cocktail lounges, two week-end nights in each location. Observations were obtained of 175 subjects in beer parlors and 240 in lounges.

In order to determine in a preliminary way some notion of the amount of drinking by patrons prior to and subsequent to a particular visit to a drinking establishment, patrons were approached on their departure and invited to phone an interviewer some evening of the following week. The rate of completed interviews was approximately 20% of those approached and the total number of interviews is expected to be about 200. The interview schedule was brief, but included information on distance travelled, mode of transportation, prior and subsequent drinking, nature of the occasion, subjective intoxication, and basic demographic information.

The collection of the data summarized above was completed by the end of March, 1976. We are now in the process of coding the data for analysis, which will continue during the spring and summer of 1976.

....continued on attached sheet

We intended to explore the possibilities of obtaining similar data from a sample of parties in private homes. We established a potential sample of 100 persons who agreed to consider notifying us when they gave a party where drinking would occur. Volunteers will have the option of providing us with three levels of information:

1) An estimate of the total alcohol available, total consumed, its form, total number of guests, and duration of party;

2) the above, plus a voluntary questionnaire for each guest in which he reports personal consumption, and other auxiliary information;

3) the above, plus allowing a team of observers to attend and record observational data.

Items (1) and (2) have been obtained from one such party to date. Returns are also both because of normal attrition expected from voluntary samples and also because such occasions occur naturally at a relatively low rate (although this rate is essentially unknown). The potential sample was established only in February. We intend to pursue this source of data as time and funds permit over the next few months, but are pessimistic about the volume of data that will ultimately be generated under the current grant. Such data, supplemented by data from parties staged or financed by us, will be the major objective of a future research project.

Relevant Publications: Cutler, R.S. and Storm, T. Observational Study of Alcohol Consumption in Natural Settings: the Vancouver beer parlor. J. Studies on Alcohol, 1975, 36, 1173-1183.

(This article reports the results of a previous study of which the project abstracted above is an extension.)

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
J.E. TONG J. Tong	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Guelph, Guelph, Ontario.

PROJECT TITLE – TITRE DU PROJET
Effects of Ethanol and Tobacco on Human Performance and Physiological Variables.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-77	$25,800.00	519-824-4120 x 3510.

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[ ] BIOMEDICAL – BIOMEDICALE
[X] BEHAVIORAL – COMPORTEMENT
[X] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

1. Research Project The purpose of the project is to examine the effects of moderate to high dosage levels of ethanol and tobacco, individually and jointly, on human subjects. Our earlier work indicates that moderate doses of alcohol produce relatively little impairment in smokers, particularly if tobacco is taken with ethanol, and there are marked differences between smokers and non-smokers for the performance effects of ethanol. The heart-rate, however, is stimulated by both drugs in a summative fashion. The current proposal is to examine the effects of higher doses of ethanol (blood alcohol levels of 0.08% - 0.12%) in smokers continually smoking, smokers deprived of tobacco and non-smokers on auditory discrimination, temporal judgment, psychomotor performance, and psychophysiological variables. The heart rate will be monitored and data for the ascending and descending limbs of the blood alcohol curve will be compared. The two main objectives are to determine the point on the blood alcohol scale for smokers at which the depressive effect of ethanol on performance and heart-rate clearly becomes apparent, and the effects of nicotine dissipation.

The rationale for the project lies in the association between usage of the two drugs, and the relationship between excessive consumption of both substances in clinical conditions such as alcoholism, oral cancer and stress diseases.

When more is known of the effects of the joint administration of these substances, it is possible that a dependency link may be hypothesised, and at the very least the findings will contribute to public awareness of associated problems.

Future directions will explore a joint dependency hypothesis.

Submitted for publication

1. Tobacco smoking, personality and sex factors in auditory vigilance performance. (to British Journal of Psychology)
2. Combined effects of tobacco and caffeine on the components of choice reaction time, heart rate and hand steadiness (to Psychopharmacologia)

Statement of unpublished findings

1. Tobacco smoking, personality and sex factors in auditory vigilance performance.

   Abstract: A total of 120 university students comprising equal groups of male and female non-smokers, smokers not smoking and smokers smoking, were compared for performance on a 60 minute auditory vigilance task. Non-smokers consistently detected more signals throughout the test. A significant interaction showed that while non-smokers detected fewer signals as the test progressed, smokers smoking increased their number of detections. There were no sex differences and no overall EPI differences in scores, although extraverted non-smokers gave significantly higher scores than introverted non-smokers with the converse being present for smokers. The results are discussed in relation to hippocampal functions.

2. Combined effects of tobacco and caffeine on the components of choice reaction time, heart rate and hand steadiness.

   Abstract: Eight male smokers were tested under 6 conditions comprising the combinations of 200 mg. caffeine or no caffeine, with no cigarette, one 0.3 mg. nicotine cigarette or one 1.3 mg. nicotine cigarette, for decision time and motor time scores on a choice reaction time task. Heart rate was monitored from a pretest period throughout the session, and hand steadiness measured on repeated occasions. Decision time scores were significantly increased by both caffeine and nicotine, but no interaction was found. The high nicotine cigarette had the greatest effect. Motor time scores were improved by caffeine only. Both caffeine alone and nicotine alone accelerated the heart rate, but in combination appeared to have antagonistic effects. Hand steadiness was significantly impaired by both drugs, but with no interaction.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
M. Vogel-Sprott	Psychology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
University of Waterloo, Waterloo, Ontario

PROJECT TITLE — TITRE DU PROJET
Social Drinkers: self-titration training effects on attitudes and use of alcohol; factors determining behavioural effects of alcohol

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
March 1974-76	$24,381	885-1211, ext 2666

FIELD OF RESEARCH SUJET DE LA RECHERCHE

EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	[X] BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
[ ]	[ ]	[X]	[ ]	[ ]

The project involves a series of studies, all concerned with aspects of the social use of alcohol. Laboratory experiments, using social drinkers, investigate possible long-term effects of receiving training in blood alcohol discrimination and self-titration. These studies examine change in attitudes and use of alcohol as well as the ability to maintain accurate discrimination and self-titration skills one year after training. Individual differences in retention of these skills also are examined since this training is considered to have relevance to controlled moderate drinking training of problem drinkers. Another series of studies manipulate factors which may importantly determine the degree of impairment occasioned by socially relevant doses of alcohol (e.g., rate at which the blood alcohol concentration rises; repeated performance of a task under low doses of alcohol).

Completed studies to date suggest that naive subjects (Ss) are slightly, but not significantly poorer in blood alcohol discrimination and self-titration than are Ss one year after they have been trained in these skills. Although this trained group as a whole revealed marginal evidence for retention of their skill, individual differences were marked and further research is needed to identify characteristics (e.g., age, drinking habits, etc) which may be associated with an ability to maintain accurate discrimination and self-titration of the alcohol dose. The evidence also suggested that the initial training procedure (one breathalyzer feedback session may be too brief. Although Ss demonstrate learning under this training procedure, more feedback training trials may be required in order to establish the learned response strongly enough to be retained over a long period of time.

Factors determining behavioural impairment under low blood alcohol concentrations (bac) are being investigated. One completed experiment examined repeated performances of a task under low bac. Training on the task was administered until drug-free asymtotic performance was established. Then the task was performed under four alcohol test sessions spaced over an 8-week interval. The initial alcohol test revealed marked impairment but successive tests showed consistently diminished impairment; drug-free performance remaining constant over these tests. The evidence suggests that the impairment of a well learned task occasioned by an initial low dose of alcohol, is not permanent. The degree of task exposure to alcohol must be considered in predicting the drug-induced behavioural effects. Social drinkers repeatedly performaing a well-learned task under low bac appear to learn to compensate for the drug effects and research examining factors which elucidate or determine this learning mechanism are underway.

PUBLICATIONS

Lightfoot, L. Discrimination of low blood alcohol levels and self-titration skills in normal males: A follow-up investigation. MASc Research Project, University of Waterloo, 1975.

Ogurzsoff, S. & Vogel-Sprott, M. Low blood alcohol discrimination and self-titration skills of social drinkers with widely varied drinking habits. Canadian Journal of Behavioural Science (in press).

Vogel-Sprott, M. Self-evaluation of performance and the ability to discriminate blood alcohol concentrations. Journal of Studies on Alcohol, 1975, 36, 1-10.

Vogel-Sprott, M. Change in performance under repeated low blood alcohol tests. Journal of Studies on Alcohol (in press).

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DEPARTEMENT
Byron S. Wenger	Anatomy

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

University of Saskatchewan, Saskatoon, Sask.

PROJECT TITLE – TITRE DU PROJET

Drugs and behavioral teratogenesis

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
Oct. 1/75 - Mar. 31/76	$8,230.00	306-343-2460

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

☐ EVALUATION – ÉVALUATION ☐ BIOMEDICAL – BIOMEDICALE ☒ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The research project is based on the proposal that drugs or other environmental agents at concentrations that produce no visible malformations may still affect the developing nervous system so as to result in permanent behavioral abnormalities. The initial objective was to establish a model system that could serve for general screening of drugs and other agents for risk of behavioral teratogenesis.

The chick embryo was selected as a test organism for the following reasons:
1) the usual reasons of ready availability, ease of manipulation and low cost;
2) three levels of behavioral development have been studied and normal patterns established. These levels are (a) early, uncoordinated movements of the embryo; (b) highly coordinated and precisely directed movements involved in hatching and (c) post-hatching problem solving ability.

The choice of nicotine as a test drug for initial studies is based on 1) it is a drug to which large numbers of pregnant women are exposed and which readily crosses the placenta, 2) it is well-established as a morphological teratogen in the chick and several mammalian embryos, and 3) while data for human teratogenicity are of marginal significance and are still being challenged, maternal smoking has been reported to be involved in both morphological and behavioral abnormalities in infants and children.

The experimental procedure involves administering single non-teratogenic (by morphological criteria) doses, at different times during incubation, or a series of still smaller doses at intervals, directly to the blastoderm or chorio-allantoic membrane of chick embryos. The drugs are administered through a hole (approx. 20 mm) in the shell. The hole is sealed with a cover glass window through which subsequent observations of embryonic movements are made. Movements are observed visually and scored by pressing a telegraph key coupled to an event recorder.

Hatching behavior is evaluated by 1) recording hatching success and observing the degree to which the hatching position was assumed in those embryos which fail to hatch and 2) direct observations of hatching movements performed by chicks exposed by opening the egg at the appropriate time.

Post-hatching behavior is evaluated by measuring overt activity in an open field test and measuring total time required for a series of trials in a detour learning test.

Key findings are:
1) Although all voluntary muscular movements are blocked for extended periods of time which vary with dosage, once the embryos have recovered we are unable to detect any differences in activity (expressed as percentage of time spent in activity phases) between control and nicotine-treated embryos during the early activity period. Even if the dosage is increased to a level which produces visible malformations, the frequency of twitches in the malformed embryo is the same as that of normal movements in controls.

Hatching behavior as judged by hatching success and the degree to which chicks which fail to hatch have assumed the normal position appears to be deficient in nicotine treated embryos. We are just beginning a study of the hatching movements in exposed embryos.

Although the detour training test used is capable of demonstrating highly significant differences in behavior between chicks of different breeds, we have been unable to detect any differences in post-hatching behavior between nicotine-treated and control chicks.

Significance of the results should be considered separately for the different levels of behavior observed. The failure of prolonged paralysis to affect subsequent embryonic behavior suggests that the classical observation that behavior patterns differentiate independently of function applies to higher vertebrates as well as to amphibians. The absence of an effect of prenatally administered nicotine on post-hatching behavior suggests that this observation may be extended to later behavior as well. We are unable, however, to eliminate the possibility that birds whose post-hatching behavior would have shown an effect were selectively eliminated by the high hatching mortality observed among treated embryos.

The high hatching mortality observed with nicotine-treated embryos appears to be related to a delay in the decline of early uncoordinated embryonic movements. The latter interfere with the precise movements involved in positioning the embryo for hatching. This decline normally occurs at the time when enzymes involved in GABA (Gamma amino butyric acid) metabolism appear in appreciable quantity. Since other cholinomimetic drugs have been observed to interfere with the GABA system, it is suggested that the observed effect of nicotine may result from interference with development of a GABA mediated inhibitory system.

The most promising direction for future work would appear to be a study of GABA levels and activities of enzymes involved in GABA metabolism in the nicotine-treated embryos.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
F. C. ADAM	CHEMISTRY
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Calgary, 2920 - 24th Avenue N.W., Calgary, Alberta, Canada T2N 1N4.	
PROJECT TITLE – TITRE DU PROJET	
New Methods in Immunoassays Using Fluorescent Labels	

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
2 of 3	13,695	284-5368

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Brief Description: To determine whether a rapid, portable and inexpensive drug analysis kit was feasable using fluorimer labelled haptens and an immunoassay system which depends on differences in fluorescence polarization ratios between bound and unbound haptens.

2. Statement of Problem:

   a) Synthesize in high purity a satisfactory dye capable of being coupled to a drug metabolite.
   b) Synthesis in high purity of a satisfactory hapten (a substituted amphetamine).
   c) Couple dye to hapten with various lengths of intermediate chain via amidic or thiocarbamate linkages.
   d) Because of the expense of antibody preparations, devise a system which will work with small amounts of material.

3. Key Findings:

   a) Interest has centered on the rhodamine and rosamine dyes since they have efficient fluorescence and absorb strongly mercury arc light at 587 nm. When prepared by conventional fusion methods the products dye cannot be isolated free from extraneous colored matter and impurity fluorescence. Using adaptations of Riggs method (Am. J. Path 34 1081 (1958) we can now isolate the dyes of interest in good yield and high purity and with no fluorescent side products. We have obtained satisfactory dyes from succinic, mellitic, iodosuccinic and mallic anhydrides, as well as various para substituted rosamines.
   b) We have experienced considerable difficulty in devising a satisfactory preparation of p-derived amphetamines which did not involve large amounts of restricted materials. In making the para carboxy derivative, one cannot use $LiAlH_4$ to reduce the nitrostyrene to the amphitamine. Catalic hydrogenatim over Pt/C, Pd/C or PtO_2 in a variety of solvents resulted in either the ketone or oxime;Zn and HCl or HAC gives unresolvable mixtures. Na in alcohol gives crude mixtures of ketone, oxime and unchanged material. These difficulties were not foreseen.
   c) Tests have been conducted on Rhodamine B, Nitrorosamine B and aminorhodamine B using a standard Aminco Bowman Spectrofluorimeter and various sample configurations. These dyes in water or glycerol can give reliable fluorescence and polarization measurements down to picomolar amounts,in samples smaller than .2 ml. It has been ascertained that there are no surface effects with respect to the polarization measurements due to adsorption of the dye at the glass liquid interface. The instrument was used in the name of convenience and can be much improved as to sensitivity, cost, and size.

4. Significance: With the successful culmination of this project, there will be available a rapid (to the order of minutes) assay method for the detection of drug or poison metabolites which could be readily used in the field or at hospitals where no expensive laboratory facilities are available (e.g. FRAT, mass spectrometers, radiation detectors, etc.) The method could be used by non-technical personnel.

5. Relevance: This project is not aimed at reducing the problem of non-medical drug use, but rather a rapid assay method for determining when, to what extent, and in what mode it has occurred.

6. Future Directions: To conclude this project, it will be yet necessary to devise and effec a satisfactory synthesis for the dye-hapten covalent coupling, and to test effectiveness of the method with chemical samples.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER / NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DÉPARTEMENT
Dr. Z. Amit	Psychology, Center for Research on Drug Dependence
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Concordia University, 1455 de Maisonneuve W., Montreal, Que. H3G 1M8	
PROJECT TITLE – TITRE DU PROJET	
Aversive and Reinforcing Mechanisms of Drug Dependence	
YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
1974-75	$8,000
	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE 514-879-7218

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Self-administered drugs were recently shown to have both reinforcing and aversive properties. It has been suggested that catecholamine systems may be involved in the mediation of both of these aspects of drug action. In view of the above, this project was undertaken to investigate the more specific elements in the interaction between aversion and reinforcement in the determination of drug self-administration. The project makes use of three experimental paradigms: conditioned taste aversion, extinction of one-way active avoidance, and voluntary oral drug intake.

In the first experiment of this project, we found that inhibition of the enzyme dopamine-beta-hydroxylase and the subsequent depletion of norepinephrine produced a marked reduction in voluntary ethanol intake in rats. In the second experiment we found that the same neurochemical manipulation which reduced drug intake was also capable of blocking the acquisition of a conditioned taste aversion. In the third experiment, we tested some of the hypotheses generated on the basis of findings collected in the earlier experiments. We examined the possibility that attenuation of a conditioned taste aversion by pre-exposure may be a predictive tool in assessing self-administration liability of drugs. We examined two experimental compounds (butorphanol and oxylorphan) supplied to us through the generosity of Bristol Laboratories, and on the basis of the effect of exposure to these drugs on subsequent performance in a conditioned taste aversion paradigm and an extinction of avoidance paradigm made predictions about their self-administration liability. We found that our results matched the results obtained by Bristol Laboratories in clinical trials.

The significance of this project is threefold: it furthers our understanding concerning the neurochemical mechanisms underlying the affective properties of self-administered drugs. It opens new avenues for research on the development of treatment procedures for drug-abusers, and finally, it may aid in the development of a rapid, simple procedure for determining self-administration liability of new compounds.

On the basis of our findings we are now planning to investigate the development of a treatment model for alcoholics.

Publications

Dorsal vs ventral lateral hypothalamic lesions: differential effects on voluntary ethanol consumption in rats. Submitted to Journal of Studies on Alcohol. With R.G. Meade, D.E. Levitan, & J. Singer.

Blockade of oral morphine intake in rats by hypophysectomy. Behavioral Biology, in press. With D. Ziskind.

The relevance of recent animal studies for the development of treatment procedures with alcoholics. Drug and Alcohol Dependence, 1975, 1, 3-13. With E.A. Sutherland.

The lateral hypothalamus, catecholamines and ethanol self-administration in rats. In M.M. Gross (Ed.), Alcohol Intoxication and Withdrawal, Vol. II. Plenum, New York, 1975. With R.G. Meade and M.E. Corcoran.

Suppression of ethanol intake following administration of dopamine-beta-hydroxylase inhibitors in rats. Submitted for publication. With D. Levitan and K. Lindros.

Ethanol and morphine self-administration: A possible relationship based on differential involvement of catecholamines. In J.D. Sinclair (Ed.), The Effects of Centrally Active Drugs on Voluntary Alcohol Consumption. Finnish Foundation of Alcohol Studies, Helsinki,1975. With D.E. Levitan.

Reduction in ethanol intake by dopamine-beta-hydroxylase inhibition. Eastern Psychological Association, New York, 1975. With R.G. Meade.

Simultaneous induction of reward and aversion produced by morphine injections in rats. Eastern Psychological Association Meeting, 1976. With L. Sklar, R. Gelfand, N. White.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
G.D. Bellward, & Dr. Abbott	Div. of Pharmacology and Toxicology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Faculty of Pharmaceutical Sciences, U.B.C., Vancouver, B.C. V6T 1W5	
PROJECT TITLE – TITRE DU PROJET Effect of Methadone, Dieldrin and other Drugs on Rat Hepatic Microsomal Epoxide Hydrase and Aryl Hydrocarbon Hydroxylase	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER – NUMÉRO DE TELÉPHONE

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Studies were initiated to find a series of compounds which might selectively increase or decrease the activities of epoxide hydrase (E.H.; determined with styrene oxide) and aryl hydrocarbon hydroxylase (AHH; determined using benzpyrene). Male rats exposed to 25 ppm dieldrin in their diet exhibited a 2.5-fold increase of EH over control levels after 2 weeks. AHH was not elevated at any time period (0-30 days) or dose (0-25 ppm). Methadone (M) was added to the drinking water of adult rats in increasing amounts up to a final dose of 85 mg/kg day in the 4th week. Female rats were found to exhibit an increase in AHH to 222% of control levels. No change in EH activity occurred. In contrast, male rats exhibited an increase in EH (156% of controls) with no change in AHH. Results were similar in newly-weaned animals. This suggests that the sex differences seen may be imprinted during fetal development or early life. Concurrent administration of M with other drugs (e.g. phenobarbital sodium, 3-methylocholanthrene and alcohol) was also studied. Phenobarbital and 3-methylocholanthrene produced additive effects with M on EH activity in male rats. Results are too preliminary to determine the mechanism of induction by M as yet.

(Supported by M.R.C. and N.M.U.D.)

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Birmingham, M.K. and Bartova, A.	psychiatry, McGill University

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Allan Memorial Institute, 1033 Pine Avenue West, Montreal, Que. H3A 1A1

PROJECT TITLE – TITRE DU PROJET

Effects of Δ^9-THC on mitochondrial respiration.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-75 -1975-76	$13,430 9,660	842-1251, ext. 1614-1617

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

☐ EVALUATION – ÉVALUATION ☒ BIOMEDICAL – BIOMÉDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The continued investigation of the effects of cannabinol derivatives on mitochondrial respiration has disclosed statistically significant differences between the inhibitory action in vitro of Δ^9-THC on NADH oxidase activity derived from rat cerebral cortex and that derived from a region composed of hypothalamus plus thalamus plus midbrain with intermediate effects obtained by mitochondria derived from the medulla or the cerebellum. At a concentration of 10^{-5}M, brain tissue was inhibited by 45-60%, an effect greatly in excess of that obtained with a similar concentration of deoxycorticosterone, a classical inhibitor of this enzyme system, which reduced the activity by only 20-30%. A similar differential was apparent with mitochondria derived from heart.

Δ^9-THC inhibited malate-glutamate-supported respiration of intact ADP-avtivated liver mitochondria from male rats at concentrations as low as 10^{-9}M. In thirteen experiments conducted in the presence of 10^{-9}M to 10^{-7}M Δ^9-THC the inhibition averaged 39 + 4% (range 17-60%). The inhibitory effect of Δ^9-THC on succinate supported respiration was minimal, averaging 6 + 1% (range 2-16%) in fourteen experiments at concentrations of 10^{-8}M to 10^{-4}M.

In vivo administration of Δ^9-THC to immature normal male rats at a daily dose of 3 mg/kg i.p. for 8 days caused a slight and statistically not significant inhibition of 20% on day 1 and 2, and an increase of 15% on day 8 of NADH oxidase activity isolated from heart mitochondria. The NADH oxidase activity of brain was reduced by over 50% on days 1 and 2 and again increased by 10% on day 8, but the findings with this tissue need to be replicated to attain statistical validation.

The increase in body weight of the immature male rat treated with Δ^9-THC at a daily dose of 3 mg/kg was identical with that of the placebo treated controls. A significant hypertrophy of the liver and involution of the thymus was noted after 8 days exposure to this dose. Plasma corticosterone levels rose dramatically on days 1, were still markedly elevated on day 2 and returned to normal by day 8.

Future work will delineate more precisely, the effects of various cannabinol derivates administered in vivo on brain mitochondrial metabolism and on pituitary-adrenal function. The excessive rise in circulating corticosterone levels is relevant to problems associated with the use of these drugs since it could indicate that some of their actions are secondary to an increase in adrenocortical hormone secretion. Our immediate aims are to establish whether the attenuation of the responses to in vivo administration is a function of peripheral catabolism (suggested from the observed liver hypertrophy), to ascertain whether acute responses can be reinstated by a period of abstinence from the drug, and to compare the effects of various cannabinol analogues in brain mitochondrial metabolism and pituitary-adrenal function.

Publications:

Bartova, A. and Birmingham, M.K.; Effects of tetrahydrocannabinol and deoxycorticosterone (DOC) on brain and adrenal NADH--oxidase activity. Federation Proc. 31, Abstract No. 1505, 1973.

Birmingham, M.K.: Reduction by Δ^9-tetrahydrocannabinol in the blood pressure of hypertensive rats bearing regenerated adrenal glands. Br. J. Pharmacol. 48, 169-171, 1973.

Bartova, A. and Birmingham, M.K.: Site of Δ^9-tetrahydrocannabinol (Δ^9-THC) inhibition in the electron transport chain. Proc. Canad. Fed. Biol. Soc., 17, Abstract No. 72, 1974.

Birmingham, M.K. and Bartova, A.: Effects of cannabinol derivatives on blood pressure, body weight, pituitary-adrenal function and mitochondrial respiration in the rat. In: Marihuana: Chemistry, Biochemistry and Cellular Effects. Editor: G.G. Nahas, 1976, by Springer-Verlag, New York Inc., p. 425-438 (In press).

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
Alan A. Boulton

DEPARTMENT – DÉPARTEMENT
Psychiatry and Psychiatric Research

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University Hospital, Saskatoon, Saskatchewan

PROJECT TITLE - TITRE DU PROJET
Identification and Quantitative Analysis of Amphetamine and some of its Metabolites and their Effect on Certain Trace Amines

YEARS FUNDED - ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED - SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
Since April 1975	$20,700 + $9,277	(306) 343-5155

FIELD OF RESEARCH SUJET DE LA RECHERCHE

EVALUATION ÉVALUATION	BIOMEDICAL BIOMÉDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
☐	X	☐	☐	X

Amphetamine, taken in large chronic doses, is capable of producing a schizophreniform psychosis virtually indistinguishable from acute paranoid schizophrenia. For this reason, amphetamine has been suggested as the best drug model for this particular psychiatric disorder. A knowledge of the fundamental mechanisms responsible for the production of above described drug induced behavior patterns would be of considerable value with respect to an understanding of and, perhaps for the eventual treatment of schizophrenia. In our laboratory we have used the MS 902S high resolution double focussing mass spectrometer and the associated integrated ion current analytical technique to examine the metabolism and distribution of d-amphetamine in several species of laboratory animals and to determine the effects of amphetamine upon the distribution and concentration of various of the 'trace' amines (ß-phenylethylamine, m- and p-tyramine, tryptamine) in brains and selected brain regions of the rat following acute and chronic amphetamine treatment. As these amines are related structurally to amphetamine and possess amphetamine-like properties it was postulated that they might possess physiological properties and functions that could be mimicked, or exaggerated, by amphetamine.

We have shown that amphetamine is converted to para-hydroxyamphetamine in both the rat and the mouse but to different extents. Both amphetamine and p-hydroxyamphetamine have been detected in all peripheral organs and brain regions examined to date. After both acute and chronic treatments, amphetamine itself was distributed essentially homogeneously throughout the brain. para-Hydroxyamphetamine, on the other hand, became concentrated in the striatum and olfactory tubercles. Analyses performed after the placement of electrolytic lesions showed that the striatal accumulation of p-hydroxyamphetamine was dependent upon an intact nigro-striatal pathway. Such findings suggest that p-hydroxyamphetamine in the striatum may act as a "false transmitter", may contribute to the development of tolerance and may be involved in the production of abnormal behavior.

The concentration of certain of the 'trace' amines in some brain regions was also affected by amphetamine. Acute injections of amphetamine caused highly significant changes in the levels of m- and p-tyramine in those brain regions rich in dopamine. These changes

however, seem not to be explainable in terms of dopaminergic function. Following chronic drug treatment behavioral tests showed the emergence of tolerance. This phenomenon appeared to relate directly to p-tyramine which increased to its pretreatment values. It appears possible therefore that p-tyramine is intimately involved in the production of some amphetamine-induced behavioral changes and in the development of tolerance to these effects.

The above results appear to indicate that behavior changes occur in parallel with changes in the brain content of some 'trace' amines. That this may be important is suggested as a result of our knowledge that these endogenous amines are pharmacologically and behaviorally active, are known to mimic the effects of amphetamine and have been shown to be excreted abnormally by some psychiatric and neurological patients.

Investigations aimed at establishing the time course and dose-response curves of these effects are in progress as are studies on the effect of drug withdrawal upon cerebral 'trace' amine content.

Publications

A.A. Boulton
'Amines and Theories in Psychiatry' Lancet 2 (1974) 7871.

T.J. Danielson and A.A. Boulton
'Detection and Quantitative Analysis of Amphetamine' Biomedical Mass Spectrometry 1 (1974) 159-162.

T.J. Danielson and A.A. Boulton
'Distribution and Occurrence of Amphetamine and p-Hydroxyamphetamine in Tissues of the Rat after Injection of d-Amphetamine Sulfate' Eur. J. Pharmacol. (in press).

T.J. Danielson, B.A. Davis and A.A. Boulton
'Species Variation with Respect to the Metabolism and Excretion of d-Amphetamine Sulphate and N-Hydroxyamphetamine Succinate' (submitted).

T.J. Danielson, T.B. Wishart and A.A. Boulton
'Amphetamine Induced Changes in Intracranial Self-stimulation (ICSS): A Possible Role for p-Tyramine' (submitted).

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
Alan A. Boulton

DEPARTMENT – DÉPARTEMENT
Psychiatry and Psychiatric Research

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University Hospital, Saskatoon, Saskatchewan S7N OW8

PROJECT TITLE – TITRE DU PROJET
Identification and Quantitative Analysis of Certain Condensation Substances formed from Alcohol and Aryl Alkyl Amine Metabolites

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
since 1974	$20,700 + $9,277 (1975-76)	(306) 343-5155

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[X] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The following alkaloid substances, 1-methyl-6,7-hydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol, from dopamine) 1-methyl-1,2,3,4-tetrahydro-beta-carboline (from tryptamine), 1-methyl-6-hydroxy-1,2,3,4-tetrahydro-beta-carboline (from serotonin) and 1-methyl-6-methoxy-1,2,3,4-tetrahydro-beta-carboline (from 5-methoxytryptamine) have been synthesised by the Pictet-Spengler condensation reaction using both conventional precursors and precursors labelled with deuterium. Each has been converted to its mono- or bi-functional dansyl (1-dimethylaminonaphthalene-5-sulphonyl) derivative. The thin layer chromatographic properties of these derivatives have been established as well as their characteristic mass spectra. The minimum quantitative detection levels have also been established using the mass spectrometric (MS) integrated ion current (IIC) technique. The bi-functional derivatives could be detected at 10^{-11} moles. Mono-functional derivates (i.e. mixed methyl ether mono-dansyl products) could be detected at the 10^{-13} moles level.

In the analysis of some urines obtained from alcoholics (3 to date) using deuterated 6,7-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinoline as an internal standard, salsolinol (as its mono-dansyl derivative) could not easily be detected or quantitated when the non deuterated and deuterated molecule ions at 440.1770 and 443.1958 respectively were compared by the MS-IIC technique.

In attempts to increase further the sensitivity of the method and to examine in more detail the methods used by others who have claimed to have identified salsolinol in the urine of Parkinson patients who had consumed alcohol, we have begun to develop a gas chromatographic procedure based on the use of heptafluorobutyrated derivatives and an electron capture detector. We anticipate a sensitivity comparable to or greater than that of the IIC procedure and to date the mixed derivative N-heptafluorobutyryl-1-methyl-6,7-methoxytetrahydro isoquinoline has been detected at the level of 2 picograms. In the event that this procedure proves to be suitable on a routine basis the identity of the substances separated on the gas column will be checked by interfacing the GC with the mass spectrometer.

It is evident that some of the earlier claims with respect to relatively high concentrations of certain alkaloids in body fluids must now be viewed with suspicion. As a consequence a reliable, sensitive and unambiguous isolation and analytical procedure is required before any investigation of interesting clinical specimens may be undertaken.

Publication

D.A. Durden, T.J. Danielson and A. A. Boulton. Tetrahydroisoquinoline and Beta Carboline Alkaloids as Their Dansyl Derivatives. In, 'Mass Spectrometry in Biology and Medicine'. Raven Press (in press).

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Ian R Brown I.R.Brown	Zoology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Toronto, Scarborough College, West Hill, Ontario

PROJECT TITLE – TITRE DU PROJET
Effect of psychotropic drugs on gene activity in neural tissue

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1973-74, 1974-75, 1975-76	$10,000, $10,000, $13,300	(416) 2843224

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Studies on psychotropic substances have focused on the psychological and physiological effects of these drugs. Less is known of their effect on the biochemistry of the brain. Further information which identifies which metabolic processes are being affected could assist the judgement of whether use of these drugs is harmful to individuals. The following is a summary of studies we have carried out on the effects of LSD on the mammalian brain.

a) Effect of LSD on RNA synthesis in the rabbit brain

The objective was to determine whether transcription in the brain was affected by the intravenous injection of LSD. Nucleotide pool size difficulties are often inherent with determinations of RNA synthesis in vivo in which incorporation of H^3-uridine is measured in control and experimental animals. To circumvent this problem we used an isolated nuclei system. LSD was injected at 100 µg/Kg into the ear vein of a young rabbit. Visible physiological changes, i.e., hyperventilation and pupil dilation were produced. After 2 1/2 hours brain nuclei were purified and assayed for template ability in an in vitro RNA synthesis assay. LSD stimulated transcription in midbrain and cerebral hemisphere nuclei when expressed over saline control values. Both nucleoplasmic and nucleolar RNA synthesis were increased. The main activity in the isolated nuclei assay was due to nucleoplasmic RNA polymerase since α-amanitin reduced synthesis by over 70% in either drug or control treatment.

b) Effect of LSD on brain chromosomal proteins

As covalent modification chromosomal protein may be prerequisite to a change in gene activity, we examined the acetylation of histones at a period 30 minutes after intravenous injection of LSD at 10 and 100 µg/Kg to young rabbits. We observed a stimulation of acetylation of total histones in the midbrain and cerebral hemispheres. Evidence for the stimulation of acetylation in individual histone bands was obtained after separation by electrophoresis on polyacrylamide gels.

c) Effect of LSD on the protein synthesis apparatus of the brain

To determine whether LSD effects the protein synthesis apparatus, polysomes were isolated from 3 major regions at various time points following intravenous injection of LSD. Polysomes were then fractionated on sucrose gradients to analyze for disaggregation of polysomes to monosomes. We employed LSD dosages which were comparable to those which cause distortion of sensory perception in humans. The drug induced a marked disaggregation of polysomes after 30 to 60 minutes with a return to normal levels by 4 hours. This transient polysome shift was not caused by RNase degradation and during maximal disaggregation there was a measurable decrease in protein synthesis. Polysome disaggregation by LSD appeared to be specific for brain cells as spleen and kidney polysomes were not effected. Others have reported that the neurotransmitter receptors for dopamine and serotonin appear to mediate the disaggregation of rat brain polysomes which is induced by high dosages of their amino acid precursos L-dopa

and 5-hydroxytryptophan. LSD is known to affect neurotransmitter receptors. Our next step will be to examine the effect of specific neurotransmitter blockers on the disaggregation of brain polysomes by LSD. Our preliminary experiments suggest that blockage of specific receptor sites impedes LSD induced polysome disaggregation. One of the specific blockers is the antipsychotic drug 'chlorpromazine' which is used clinically to suppress hallucination in schizophrenia. It is also used to terminate effects of LSD in humans and reduce 'flashbacks'.

Publications

1) Brown, I.R. (1975) RNA synthesis in isolated brain nuclei after administration of d-lysergic acid diethylamide (LSD) in vivo. Proc. Nat. Acad. Sci. U.S.A., 72, 837-839.

2) Brown, I.R., and Liew, C.C. (1975) Lysergic acid diethylamide: effect on histone acetylation in rabbit brain. Science, 188, 1122-1123.

3) Holbrook, L. and Brown, I.R. (1976) Disaggregation of brain polysomes after administration of d-lysergic acid diethylamide (LSD) in vivo. In press to Journ. of Neurochemistry.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Gilles Caillé	Pharmacologie

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Hôpital Santa Cabrini - Université de Montréal.

PROJECT TITLE – TITRE DU PROJET
Création d'un centre de détection et de dépistage des drogues.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975	$11,600.00	343-7904

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
☐ EVALUATION – ÉVALUATION
☒ BIOMEDICAL – BIOMÉDICALE
☐ BEHAVIORAL – COMPORTEMENT
☐ SOCIAL SCIENCE – SCIENCES SOCIALES
☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

La composition chimique et la pureté des différentes "drogues de la rue" demeurent un sujet d'actualité pour les gouvernements et les professionnels de la Santé. Au cours des deux dernières années, il nous est apparu que même les distributeurs et les usagers des dites drogues tentent l'impossible pour vérifier l'identité et la pureté de leur marchandise.

Un relevé de la littérature, provenant en grande partie des Etats-Unis, nous a permis de constater qu'autant d'un point de vue qualitatif que quantitatif les "drogues de la rue" sont vendues sous trompeuse identification. En effet, ce marché clandestin dispose non seulement de drogues illicites comme le LSD, le cannabis et les dérivés amphétaminiques mais aussi de médicaments comme les barbituriques, les anorexigéniques, les tranquillisants, les hypnotiques, etc. Ces drogues illicites et ces médicaments utilisés à des fins non médicales sont-ils vendus à des doses dangereuses pour les usagers? Renferment-ils des excipients ou des diluants nocifs pour la santé? Enfin, la popularité de ces drogues est-elle aussi grande qu'on veut bien nous le laisser croire? Autant de questions restées sans réponse, même si nos gouvernements et certains média d'information en ont fait un sujet d'actualité depuis quelques années. Nous croyons que la composition chimique de ces drogues devrait être rapportée afin de préciser les caractéristiques épidémiologiques régionales de ce marché illicite et alléger conséquemment la tâche des différents professionnels de la Santé lorsqu'il s'agit pour eux d'appliquer une thérapeutique rationnelle.

Depuis quelques années déjà, la littérature scientifique consacre un large chapitre au problème posé par l'usage abusif des drogues. Les intoxications médicamenteuses constituent, par leur incidence particulièrement inquiétante, les tristes exemples de cette vague de toxicophilie que connaît notre société actuelle.

Le traitement des intoxiqués s'avère une entreprise laborieuse à laquelle bien peu de nos professionnels de la Santé ont été habilités à faire face. Malgré le nombre croissant de centres anti-poison en Amérique du Nord, rares sont ceux d'entre eux qui peuvent présentement se dire en mesure d'assumer la réhabilitation psycho-sociale des toxicomanes. De fait, les énergies déployées jusqu'à maintenant ont surtout porté sur la nature des soins intensifs à administrer et sur la création de différents services d'urgence nécessaires au traitement des cas d'intoxications aigues. En dépit de tous ces efforts, on peut déplorer encore aujourd'hui le peu d'accessibilité de la plupart des centres hospitaliers de la région montréalaise aux services offerts par un laboratoire de toxicologie analytique.

Notre expérience nous a persuadés de la pertinence clinique et des précieux renseignements que rend la toxicologie analytique au clinicien, particulièrement lorsque ceux-ci s'inscrivent dans une perspective de travail multidisciplinaire harmonieux. Un tel contexte nous a permis d'établir un protocole clinique et analytique apte non seulement à faciliter la tâche du médecin lorsqu'il s'agit pour lui d'élaborer un diagnostic différentiel et de poser un pronostic clinique, mais capable aussi de vérifier l'efficacité des mesures thérapeutiques envisagées. Une telle approche constitue en soi une expérience riche en apprentissage dans des domaines aussi peu connus que ceux de la symptomatologie et de la thérapeutique toxicologique.

Toutes les substances de référence nous ont été gracieusement fournies par le Ministère de la Santé du gouvernement fédéral. Tous les échantillons reçus ont été analysés par chromatographie sur couche mince et en phase gazeuse, par spectrofluorométrie et par spectrophotométrie dans l'ultraviolet et l'infra-rouge. Les données ainsi recueillies nous ont permis de présenter les résultats suivants:

I- Drogues de la rue

L'incongruité existant entre la nature des réquisitions et la composition des échantillons constitue une réalité connue déjà de tous les centres de détection nord-américains. L'ampleur de cette disparité varie d'une part selon la drogue, la région et l'échantillonnage considérés, et d'autre part selon les fluctuations dans la nature des stocks et dans les voies de ravitaillement des approvisionneurs. Néanmoins toute proportion gardée, nos analyses nous permettent de réaffirmer la disponibilité très limitée de la mescaline sur le marché clandestin. En effet, seulement trois des 101 échantillons censés renfermer de la mescaline se sont avérés positifs, tous les autres contenant le plus souvent des dérivés amphétaminiques, de la phencyclidine ou encore du LSD.

D'un strict point de vue quantitatif, nous pouvons assumer à date que les dérivés amphétaminiques, la phencyclidine et les tranquillisants sont vendus à des doses très faibles. Par exemple, on trouve généralement des concentrations de l'ordre de 1 ou 2 mg par capsule de phencyclidine alors que les capsules de méthaqualone ne renferment que 30 à 50 mg d'ingrédient actif, soit environ le dixième d'une dose efficace.

Quant au LSD, les quantités retrouvées dans les échantillons varient de 5 à 400 mcg, cette dernière dose pouvant présenter un danger réel pour l'usager.

II- Drogues en milieux biologiques

Cinquante requêtes nous ont été adressées pour recherche d'une substance inconnue et 162 pour recherche d'une substance suspectée par le clinicien. Dans le premier groupe de requêtes, 42, soit 84% des analyses se sont révélées "positives" (présence d'une substance). Les résultats des analyses du second groupe de requêtes se présentent comme suit: 37, soit 22.8% des analyses "positives" pour l'agent suspecté, 27, soit 16.7% des analyses "négatives", 91, soit 55.6% des analyses positives pour un produit autre que celui suspecté, les autres analyses ont été irréalisables, (4.3%).

La difficulté d'établir un diagnostic différentiel des intoxications médicamenteuses sur des bases purement cliniques ressort clairement alors que le pourcentage de requêtes "positives" pour la drogue suspectée s'établit à 22.8%. Par contre, le pourcentage de requêtes "positives" pour recherche d'un agent inconnu s'élève à 84%, témoignant de l'aisance relative avec laquelle le médecin distingue un syndrome d'intoxication médicamenteuse d'un autre syndrome clinique.

Concernant la "prévalance" observée parmi ces différents types d'intoxications, nos résultats se comparent à ceux relevés sur la côte ouest américaine ou encore dans la région parisienne. Les substances sédatives et hypnotiques constituent le groupe de toxiques les plus fréquemment rencontrés, suivi par le groupe des analgésiques et des anesthésiques, et celui des antidépresseurs et des antipsychotiques, selon une fréquence à peu près semblable. L'absence notable d'intoxication due à des substances psychotiques et/ou psychodysleptiques souligne une fois de plus la contribution négligeable des "drogues de la rue" au chapitre de l'étiologie des intoxications médicamenteuses.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Dr. D.J. Campbell D.J. Campbell	Pathology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Vancouver General Hospital, Vancouver, B.C., V5Z 1M9.

PROJECT TITLE — TITRE DU PROJET
Hospital-Based Reference Drug Abuse Analytical Laboratory

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1974-1976	$46,835	(604) 876-3211

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This project involves the development of a modern laboratory facility to perform rapid positive drug identification in biological specimens and in dosage forms. The purpose of the laboratory is to provide an analytical referral base to smaller laboratories and to the medical profession in problems arising from drug dependance, and to co-operate with federal and provincial drug identification laboratories. It will provide laboratory support to investigators conducting epidemiologic studies, effects of drugs on pregnancy and on the new-born, and for the evaluation of new treatment programs. It will also be used as a diagnostic service in emergency overdose and psychiatric admissions. With these applications the project will also assess the usefulness of a gas chromatograph/mass spectrometer in the identification of foreign toxic substances.

A Du Pont Model 21-490 F GC/MS having a resolution of 1100, a 6-inch 90° magnetic sector, and a differential pumping system, was installed. It is equipped with a dual electron impact/chemical ionization source which allows generation of mass spectra or chemical ionization spectra. The limit of the mass range is 2400 a.m.u., which can be scanned at a variable speed ranging from 1 to 1000 seconds/decade. Specimen admission may be made via an interfaced Varian GC (SE-30 column), heated batch inlet, or temperature-programmed direct probe. In the absence of a data reduction system, a Bell and Howell 5-134 oscillographic recorder capable of recording 1000 peaks per second is used.

Considerable time was devoted to studying the effects of ion pressure and source temperature. The optimum ion pressure selected for most analyses is 0.6 Torr using isobutonium ion. Thermal degradation of morphine was significant if the source temperature exceeded 175°.

A number of sample preparation techniques for direct probe analysis was investigated with concern for cleanness of extract, speed, efficiency of recovery and size of sample required. The selected method was a modification of Meola's charcoal extraction technique (Clin. Chem. 20(2):184, 1974). Typical sensitivities in urine by direct probe using a 10 ml urine sample are: amphetamine 0.25 microgram/ml., barbiturate 1.0, codeine 0.5 and methadon 0.5, all in the CI mode. Admission by GC yielded sensitivities in the 50 nanogram range.

The procedure was tested on a wide representation of drugs or their metabolites in urine and was found to be rapid and reliable. In general, it is possible to arrive at a positive identification within two hours of receipt of specimen. There is, however, a lack of mass spectral data on drug metabolites, by which in many instances the parent drug must be identified.

The GC/MS approach to drug identification is practical and preferable. The equipment, however, requires precision maintenance and skilled personnel.

Work is proceeding on the identification of tricyclic anti-depressants from their urinary metabolites, as well as on the general compilation of chemical ionization mass spectra.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. D.J. Campbell D.J. Campbell	Pathology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Vancouver General Hospital, Vancouver, B.C., V5Z 1M9.

PROJECT TITLE – TITRE DU PROJET

Stability of Drugs and Their Metabolites in Urine

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-1976	$24,918.45	(604) 876-3211

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

☐ EVALUATION – ÉVALUATION ☒ BIOMEDICAL – BIOMÉDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

This study is for the purpose of determining the effect of delay on the stability of drugs, or the metabolites by which they are detected in urine in so far as drug-screening techniques are concerned. This information is necessary before specimens may be safely transmitted or stored prior to analysis. This information will also establish the feasibility of using patient-produced control specimens for local, regional or national quality control programs in drug screening from the standpoint of specimen suitability.

A number of extraction and chromatographic systems were evaluated in order to select a procedure which was both sensitive and capable of yielding reproducible sensitivity on repetitive assays. The extraction techniques examined included immiscible solvent extraction, extraction by use of cation exchange resin paper, extraction by XAD-D polymeric non-ionic resin and dye-binding. The latter procedure, as published by Stoner and Parker (Clin. Chem. 20(2):309-311, 1974) was the best suited for this purpose. A variety of chromatographic systems was evaluated and the method of Davidow was found to be superior. On 10 ml specimens the following typical sensitivities were found: amphetamine 0.25 micrograms/ml., barbiturates 1.0, methadon 0.5, morphine 1.0.

24-hour urine specimens were collected from subjects known to be on specific drug usage and aliquoted into portions which were subjected to a variety of storage conditions followed by analysis. Drugs studied were representative of the following classes: phenylethylamines, long and intermediate-acting barbiturates, glutarimide sedatives, piperidinedione hypnotics, quinazolone sedatives, benzodiazepine, carbamate, phenothiazine and rauwolfia tranquilizers, tricyclic anti-depressants, narcotic analgesics and synthetic narcotics.

At the time of writing, testing has been concluded but detailed analysis of the chromatographic and mass spectral data is incomplete. Certain preliminary generalities, however, may be made:

1. Lyophilized urine may be safely stored by refrigeration with occasional exposure to room temperatures for periods in excess of six months without artifact formation or deterioration.
2. Boric acid (8 g/l) and formaldehyde, used as preservatives, reduce the recovery of organic bases.
3. Chloroform is not a useful preservative.
4. Mercuric chloride (50 mg/l) frequently causes poor recovery due to co-precipitation of the drug with protein and complex formation with barbiturates.
5. The use of sodium fluoride or pH control is of dubious value.
6. Stored specimens frequently yield false positives for phenylethylamines from the formation of decarboxylated amino acids.
7. Storage at room temperature is preferable to refrigeration in specimens not lyophilized and is seldom improved by the addition of preservatives and results in acceptable stability.

Further general research in this area is not contemplated since adequate data has been generated to understand the problems related to delays in specimen analysis.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
CLARK, S.C.	Pharmacology & Therapeutics

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Faculty of Medicine, University of Calgary, Calgary, Alberta

PROJECT TITLE – TITRE DU PROJET
Clinical Assessment of Opiate - like Drugs and Their Antagonists in Man.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-75	$22,500.00	403 284-6830

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1) Description of Research Project:

The purpose of this study was to assess the addictive potential in man of azidomorphine, a new morphine cogener. Subjects were volunteer federal prisoners at the N.I.D.A. Addiction Research Centre in Lexington, Kentucky, U.S.A.

Subjective effects and miosis were assessed following subcutaneous administration of doses of azidomorphine bitartrate, morphine sulphate and placebo administered at weekly intervals in a double-blind, randomized block design. The Single Dose Opiate Questionnaire[1] and a questionnaire containing items from the Morphine-Benzedrene Group Scale[2] were used to measure morphine-like subjective effects and euphoria. Pupil diameter was measured photographically[3]. Measures were taken prior to drug administration and at intervals thereafter.

In addition, the ability of azidomorphine to substitute for morphine was determined with the 24 hour substitution technique[4] in subjects physically dependent on morphine sulphate, 15mg., given subcutaneously 4 times each day.

2) Summary of Key Findings:

Azidomorphine constricted pupils, produced morphine-like subjective effects and euphoria, and suppressed the morphine abstinence syndrome. Azidomorphine was 10 to 50 times as potent as morphine. It was concluded that, in man, azidomorphine is a typical morphine-like drug.

3) Significance of Project:

Animal studies and initial clinical studies indicated azidomorphine was relatively less addictive than morphine and other available narcotics. This study showed that, whereas, azidomorphine is more potent than morphine, it has a comparable addictive potential.

4) Findings Relevant to Reducing Problems Associated with Non-Medical Drug Use:

Initial findings that azidomorphine was less addictive than other narcotics could have resulted in release of the drug with inadequate controls and misleading advertising. Inadvertent iatrogenic addiction would have probably occurred as well as illegal use. A definitive study of addictive liability in man clarified the situation and identifies azidomorphine as a typical morphine-like drug.

5) Future Directions of Research Project:

i) Studies of d-propoxyphene napsylate (Darvon-N$^{R)}$ in man.

ii) Studies of narcotic antagonists as an adjunctive treatment of narcotic addiction.

References

1) Martin, W.R. & Fraser, H.F.: A. comparative study of physiological and subjective effects of heroin and morphine administered intravenously in postaddicts, J. Pharmacol. Exp. Ther. 133: 388-399, 1961.

2) Jasinski, D.R., Martin, W.R., & Hoeldtke, R.D.: Studies of the dependence-producing properties of GPA-1657, profadol, and propiram in man, Clin. Pharmacol. Ther. 12: 613-649 1971.

3) Gorodetzky, C.W., & Martin, W.R.: a comparison of fentanyl, droperiodol, and morphine, Clin. Pharmacol. Ther. 6: 731-739, 1965.

4) Fraser, H.F., & Isbell, H.: Human pharmacology and addiction liabilities of phenazocine and levophenacymorphine, Bull. Narcot. 12: 15-23, 1960.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
DR. DONALD J. ECOBICHON	PHARMACOLOGY

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
FACULTY OF MEDICINE, DALHOUSIE UNIVERSITY, HALIFAX, N. S.

PROJECT TITLE TITRE DU PROJET The placental and milk transfer of chronic low-doses of methadone, its pharmacokinetics and effects on morphological and biochemical aspects of hepatic function in the neonatal guinea pig.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1976-1978	$42,520.00	902=424-2562

FIELD OF RESEARCH SUJET DE LA RECHERCHE
☐ EVALUATION ÉVALUATION
☒ BIOMEDICAL BIOMÉDICALE
☐ BEHAVIORAL COMPORTEMENT
☐ SOCIAL SCIENCE SCIENCES SOCIALES
☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The extensive street use of methadone as well as in maintenance programmes has markedly increased the number of pregnant women receiving this agent. In addition to the withdrawal symptoms frequently observed, the question has been raised whether or not methadone might have subtle effects on hepatic enzymes in the developing neonate. Induction of hepatic microsomal, drug-metabolizing enzymes has been observed in methadone-treated animals. In view of the difficulty in obtaining proper samples from human infants, the paucity of good pharmacokinetic studies in the human and the need for an animal model comparable to the human, this research project proposes to (i) investigate the pharmacokinetics of transplacental and milk transfer of methadone in the guinea pig; (ii) quantitatively study the tissue distribution of methadone in dams and perinatal guinea pigs; (iii) examine the hepatic tissue of perinates for possible morphological changes and biochemical alterations in drug-metabolizing enzymes following passage to the perinate via the placenta and the milk; and (iv) investigate the pharmacokinetics of transplacental and milk transfer of chronic low doses of methadone in the perinatal guinea pig from 50 days gestation onward.

The data will be obtained following the acute oral administration of methadone to groups of non-pregnant female guinea pigs for 7 days at a low (2.5mg/kg) and a high (10 mg/kg) dose. Animals will be anesthetized and killed daily, providing blood, brain, liver, kidney and muscle samples for the quantitation of methadone residues by gas-liquid chromatography, morphological examination of the liver by light and electron microscopy and biochemical analysis of a group of hepatic drug-metabolizing enzymes.

Pregnant guinea pigs will receive the same oral dosage of methadone from day 50 of gestation until parturition, with animals being killed at day 60,65, and 68 (term), the tissues of both dams and foeti being removed for analysis. Untreated dams having given birth to normal infants will receive the same oral dose of methadone for 14 days in order to study the milk transfer of the drug. Suckling neonates and pigs will be killed and tissues removed for chemical, biochemical and morphological analysis.

A final study will involve the chronic administration of a selected dose of methadone to pregnant guinea pigs from day 50 of gestation until weaning, killing the dams, foeti and pups at selected intervals for chemical, biochemical and morphological analysis of the effects of methadone on hepatic development in the perinatal individuals.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Havlicek, Viktor, M. D., D. Sc.	Physiology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Faculty of Medicine, University of Manitoba, 770 Bannatyne Avenue, Winnipeg, Manitoba. R3E 0W3

PROJECT TITLE - TITRE DU PROJET Abnormalities of brain electrical maturation of sleep states in newborn infants of chronic alcoholic mothers.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED - SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
4 months, since Oct. 1, 1975	over two years, $43,000.00	204-786-3767

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Clinical and experimental data show that ethanol freely crosses the placentar barrier in man and in animals. Nevertheless previous evidence from human studies and animal experiments has not given clear indication of an association between maternal alcoholism and morphological and functional abnormalities in the offspring. Developmental delay in the body length and head circumference associated often with some other morphological abnormalities in children of alcoholic mothers has been reported only recently (Jones et al., 1973). There are no updated functional studies on infants of alcoholic mothers. The physiology and pathology of sleep in infants has attracted increasing interest in last years. Since infants and young children spend most of the time sleeping the EEG and polygraphic recording during sleep have become a new important diagnostic and research tool. Recent research in quantitative analysis of the EEG indicates the ultimate need in developing objective computerized techniques. This need was originally recognized for basic research on brain electrical activity. The same requirement has now been demonstrated for clinical EEG diagnosis. There are several methods for computer analysis of the EEG signal. Of particular importance is application of the fast Fourier transform (FFT) (Cooley and Tukey 1965) to the spectral analysis of the EEG (Dumermuth and Fluhler, 1967). Spectral analysis with the usual resolution of 0.1-0.2 cycles/second or Hertz (Hz) yields large quantities of digital data. For example, only one hour EEG in our program results in about 200,000 data points, and evaluation of such data becomes cumbersome. In order to make intraindividual and interindividual statistical analysis of the power-spectrum in different sleep stages more practical we have integrated minute spectral data into usual clinical frequency bands - delta, theta, alpha and beta: (delta 1 (1.10-1.48 Hz), delta 2 (1.56-3.5 Hz), theta 1 (3.61-5.57 Hz), theta 2 (5.66-7.52 Hz), alpha 1 (7.62-9.47 Hz), alpha 2 (9.57-12.50 Hz), beta 1 (12.60-17.48 Hz), beta 2 (17.58-25.00 Hz) and integrated EEG in frequency range 1.56-25.00 Hz. Such computerized spectral analysis of the EEG showed statistically significant changes of the EEG during sleep in correlation with brain maturation. Significant quantitative changes occurred in all three stages of sleep in newborn infants. In quiet sleep full-term infants differed from premature babies by significantly higher intensity in delta and theta frequencies (1.6-7.5 Hz). During indeterminate sleep the slowest frequencies (0.1-1.5 Hz)showed

significantly less intensity, while intensity of faster frequencies (1.6-7.5 Hz) was significantly greater in full-term infants. REM sleep differed in slowest (0.1-1.5 Hz) and fastest (17.5-25 Hz) frequency bands, showing significantly lower intensity in the former and significantly higher in the latter in full-term infants. From the diagnostic point of view the most important maturational EEG changes were found by computing the REM sleep-quiet sleep frequency spectrum difference. This showed significantly stronger intensity during quiet sleep over a wide range of frequencies (0.1-12.5 Hz) in full-term infants, while preterm neonates had an almost identical spectrum during these two stages of sleep with a significant intensity drop only in theta 2 (5.6-7.5 Hz) during REM sleep. These indices of maturation provide us with a method for describing the normal ontogeny of spontaneous electrical activity of the brain (recently published: V. Havlicek, R. Childiaeva and V. Chernick, EEG frequency spectrum characteristics of sleep states in full-term and preterm infants. Neuropadiatrie, 6, 24-40, 1975). These normal standards allow us now to compare newborn infants of varying gestational ages and birth weights with abnormalities of electrocortical maturation in newborn infants of alcoholic mothers. Since the project started (1.X.1975) we were able to monitor sleep EEGs in 9 newborn infants of chronic alcoholic mothers. Since in most of these infants repeated sleep recordings were performed therefore to date we have completed 19 examinations in infants ranging from 32 to 42 weeks gestation. These preliminary data already indicate that EEG during all three stages of sleep was abnormal particularly in slow frequency bands (delta 1 - alpha 2, see above) in 12 out of 19 examinations in infants of alcoholic mothers. Control values were obtained from healthy infants matched for gestational age. In cooperation with the Child Development Clinic (Director Dr. McRae) infants of alcoholic mothers will be examined for morphometric, neurological and intellectual development at following birth ages: six weeks, six months and then at yearly intervals up to school age. Thus abnormalities in the development of electrical activity of the brain will be correlated with subsequent neurological and intellectual development. Since infants of alcoholic mothers show underdevelopment in body growth, in cooperation with Dr. H. Friesen we intend to study levels of growth hormone in blood plasma in these infants. By using all these examinations this project is designed to make early diagnosis of abnormalities in brain development in offsprings of alcoholic mothers possible with the ultimate goal to understand the mechanism of such abnormalities. It is hoped that our study will be important in planning specific therapeutic, preventive and educational programs for such infants. Data of this project may also be helpful in designing preventive and educational programs for alcoholic mothers. This seems to be very important since majority of these mothers bear many babies.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. M. Hirst and Dr. C.W. Gowdey M. Hirst	Pharmacology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Western Ontario, LONDON, Ontario N6A 5C1.	

PROJECT TITLE – TITRE DU PROJET

Studies into behavioural, neurochemical and treatment aspects of heroin and ethanol intoxications

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-75	$86,495	(519) 679-3831

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Description of Project. The aim is to devise and study animal models for opiate tolerance and dependence. Two methods of determining analgesic activity in mice (as a measure of agonist activity) have been compared after a wide range of doses of heroin HCl. The duration of analgesia after single injections of several salts of heroin in three different vehicles has been estimated and an attempt made to compare duration of analgesia and degree of dependence, as measured by naloxone challenge. The rate of tolerance development to the analgesic effect of repeated injections of heroin given once a day or in 3 divided doses was studied and attempts made to monitor changes in physical dependence with these schedules. In rats changes in conditioned behaviour, in diurnal patterns of feeding and body temperature, and in body weight were determined after acute and chronic exposure to heroin and on withdrawal. A microanalytical method for monitoring blood levels of heroin and its metabolites is being developed.

2. Summary. Tail-clip method of measuring heroin-induced analgesia in mice is more sensitive than the hot-plate method [ED_{50} by tail-clip at 30 min. after s.c. heroin HCl was 1.0 ± 3.42 (S.E.) mg/kg and at 180 min. was 27.5 ± 3.05; by hot-plate, ED_{50}'s were 4.9 ± 3.13 and 173.8 ± 5.38 mg/kg, respectively. The curves relating changes of ED_{50} with time after injection were, however, parallel, the rate of change of the median analgesic dose being about 2%/min. The acute LD_{50} of heroin HCl in mice was estimated as 190.5 ± 3.01 mg/kg.

The mean duration of analagesia (tail clip) was 3.0 hr after heroin HCl in saline and 8.1 hr after heroin 3,5 di-tert butyl 2,6 di-OH benzoate in slow-release vehicle; 7.2 hr. for equimolar heroin pamoate in slow-release vehicle and 5.5 hr. in peanut-oil. Heroin zinc tannate in slow-release vehicle produced measurable analgesia for about 2 wk. There is a negative correlation between insoluble salt dissociation and analgesia duration. Physical dependence studies using a naloxone challenge 24 hr. post injection gave some inconsistent results. The durations of analgesia correlated with the number of jumps per mouse.

I.v. and s.c. Heroin were equivalent in analgesic potency and duration; there were parallel dose-related increases in durations of induced hyperactivity and analgesia.

The rate of tolerance development, measured by shorter analgesia durations, is dependent on total daily dose of H. When the total daily dose was given in three divided doses, tolerance developed slower. Naloxone-induced jumping proved to be a variable and insensitive method for monitoring the progressive development of physical dependence.

Low doses of H tended to stimulate bar-pressing in FR- but inhibited the performance of VI-trained rats. Higher doses reduced or blocked bar-pressing; with repeated daily doses bar-pressing increased as rats became tolerant but with wide inter-rat variability. On withdrawal, bar-pressing increased but body weight fell for 2 days.

Daily injections of 5 or 20 mg/kg heroin HCl disrupted the normal diurnal patterns of food acquisition and body temperature. As injections continued, the initial phase of no feeding progressively shortened and was followed by a period of vigorous feeding. Patterns of diurnal changes in body temperature were similar to the changes in feeding. Withdrawal caused further disruptions in feeding and temperature patterns.

A micro-method for analysis of morphine in biological fluids was developed using electron-capture detection of the di-hepta fluorobutyrate derivative. Quantitative analyses can be done with as little as 25 pg. The method was used to determine blood levels of morphine in mice after i.v. and s.c. doses, and were correlated with analgesia. The blood T 1/2 is 20-25 min. after i.v. morphine, but there was great inter-mouse variability in the blood concentration associated with analgesia. Analyses after s.c. morphine suggest that not all of a given dose appears in the blood within 3 hr.

3. Significance. The results, to date, have revealed effects of heroin previously unreported, suggest several rodent-based models for screening other opiates and for investigating the mechanisms of tolerance development, extend the sensitivity of reported analytical techniques, and point to the value of long-lasting preparations of narcotic agonists in experimental and clinical studies.

4. The relevance re NMUD of having animal models which are sufficiently economical, sensitive and reliable for rapid screening of narcotic analgesics and for studying the mechanisms involved in tolerance and dependence is obvious.

5. Future directions include the determination of whether the diurnal disruptions of feeding and body temperature induced by H are specific for other narcotic agonists; further investigation of the value of long-acting narcotic agonist preparations; the role of brain amines in the development of tolerance; extension of the microanalytical technique to other opiates.

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Smith, R.W., Hirst, M. and Gowdey, C.W. (1976). Duration of analgesia and hyperactivity in mice after single injections (s.c. and i.v.) of heroin. Arch. Int. Pharmacodyn. Thér, 222.

Thornhill, J.A., Hirst, M. and Gowdey, C.W. Effects of chronic administration of heroin on rats trained on two food reinforcement schedules. Arch. Int. Pharmacodyn. Thér. 218: 277-289 (1975).

Thornhill, J.A., Hirst, M. and Gowdey, C.W. Disruption of diurnal feeding patterns of rats by heroin. Pharm. Biochem. Behav. 4 (2) 1976.

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Herne, R., Hirst, M. and Gowdey, C.W. Blood levels and analgesia in mice following subcutaneous and intravenous administration of morphine sulphate. In preparation.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. E.A. Hosein	BIOCHEMISTRY
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
McGill University, McIntyre Med. Bldg., 3655 Drummond Street, Montreal H3G 1Y6, Quebec	
PROJECT TITLE – TITRE DU PROJET	"Hepatotoxicity of Ethanol in Rats Following Chronic Administration"
YEARS FUNDED ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
January 1, 1975 - March 1976	$23,000.	392-3019

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

In previous work we observed that the administration of acute doses of ethanol to rats cuased a decrease in oxygen consumption of the liver mitochondria from these animals. With 0.2 - 0.5 mM succinate as substrate, the decrease in respiration persisted even after the membrane of the mitochondria had been ruptured by lysolecithin. These results suggested that ethanol induced some type of membrane defect demonstrable in the intact and lysed mitochondria. In an attempt to investigate the nature of this membrane defect, we have studied the influence of chronic ethanol administration to rats on the magnesium activated ATP-ase in such mitochondria. The activity of the enzyme was assayed at different temperatures and Arrhenius plots generated from these data. It was observed that there was a distinct phase transition or temperature break in the activity of this enzyme at 18°C. With mitochondria from chronic alcohol-treated animals, the break occurred 2° lower. These data are important as they are the first to support the view that ethanol a narcotic substance induces a phase transition in membrane lipids in vivo. The Arrhenius plots also explains why other investigators obtained either no change in the ATP-ase activity of such mitochondria or in some instances, a slight increase when the assay was carried out at 37°C. An examination of these data indicate that when the assay was carried out at the lower temperatures, alcohol was shown to have caused an alteration in the mitochondrial membrane resulting in a decrease in the transition temperature. This means that compared to normal mitochondria the enzyme was now more active at the lower transition temperature. It was obvious therefore that such mitochondria were not normal. An attempt will be made to support this view further by generating Arrhenius plots of other membrane-bound enzymes such as succinoxidase.

In an attempt to assess further the damage caused by chronic alcohol treatment we have studied the capacity of such mitochondria to synthesize proteins. While other investigators have shown that the total amount of protein synthesized by the liver mitochondria from alcoholic rats is lower than that obtained from normal rats, we have observed that by separating such proteins with gel electrophoresis there was diminished amounts of the various proteins synthesized by such mitochondria. Moreover, it was observed that the turnover rate of these mitochondria was rapidly increased. Whereas the normal turnover for liver mitochondria from animals fed the Metrecal diet was 6.2 days, that from chronic alcohol-treated animals was 4.6 days. If one were to consider this increase turnover in the chronic alcoholic rats coupled with the fact that there is diminished protein synthesis, then in time this would lead to a diminution of proteins or enzymes which may be essential for maintaining normal mitochondrial structure and function. These results also suggest that if the alcohol treatment were allowed for an extended period of time, then the succeeding generations of mitochondria would certainly be defective, being deprived of their normal complement of various proteins which could have important and possible detremental metabolic consequences such as the induction of alcohol hepatitis.

In the present work it is proposed to determine whether or not the results obtained so far in this investigation could provide some insight into the hepatotoxic activity of alcohol with regard to the production of alcohol hepatitis and possibly cirrhosis. Recently other investigators have shown that it is possible to induce alcohol hepatitis and cirrhosis

in baboons. While this appears to be an ideal model for studying the hepatotoxic effect of alcohol it must be admitted that it may not be the most suitable. Since there has been criticism that the rat is also unsuitable because the induction of alcohol hepatitis and cirrhosis is difficult to achieve, we have searched the literature to determine why the guinea pig has not been used as the model for alcohol studies in the past. This inquiry was also prompted by the fact that the guinea pig, like the baboon and man, are the only species in which a vitamin C deficiency can be induced, although there is no evidence that such a deficiency might be involved in alcoholic hepatitis. Since it is well established that during the induction of alcohol hepatitis there is concomitantly an increase in proline hydroxylase activity and collagen synthesis, and an accumulation of insoluble glucosaminoglycans (GAG), we believe that the accumulation of these compounds which are normal components of connective tissue could likely be indicative of some fundamental derangement in connective tissue formation induceable in the baboon and man but not so readily in the rat. The fact that chronic alcoholism induces a depletion of vitamin C and iron may or may not be irrelevant to this derangement in connective tissue synthesis. It is therefore proposed to compare the influence of chronic alcohol administration to guinea pigs and rats on the synthesis and turnover of collagen, mitochondrial protein and glucosaminoglycans in the liver of these animals.

In previous work it has been shown that subsequent to acute administration of alcohol to rats there is mobilization of liver glycogen and an accumulation of α-glycerophosphate. We have now shown that one hour after alcohol administration the α-glycerophosphate is derived from glycogen and that part is used for triglyceride synthesis while the remainder may either be used as a shuttle substrate or accumulate in the cytosol. The question arises about the metabolic fates of the newly formed triglyceride and α-glycerophosphate. What is their rates of turnover in the presence of absence of further alcohol treatment? We propose to extend our previous studies to answer the question raised following further treatment of the animal with alcohol.

Since other investigators have shown that chronic alcohol treatment also affects normal brain function which may in part be adduced to nutritional deficiencies, we nevertheless propose to repeat with brain mitochondria some of the experiments on the influence of ethanol on the activity of membrane-bound enzymes and on protein synthesis which we have carried out with rat liver. Other investigators have already shown that brain mitochondria from chronic alcohol-treated animals have a decreased capacity to synthesize proteins. The main thrust however in our proposal would be to determine the turnover rate of such brain mitochondria and the yield of protein synthesized during chronic alcohol administration, since some investigators feel that certain diseases such as retrograde amnesia which is common in alcoholism, may well be associated with a defect and/or deficiency in brain protein synthesis.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DEPARTEMENT
Dr. E.A. Hosein	Biochemistry

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE

McGill University, McIntyre Med. Bldg, 3655 Drummond Street, Montreal H3G 1Y6, Quebec

PROJECT TITLE — TITRE DU PROJET "A Subcellular Model from Brain which likely Reflects Changes Taking Place in the CNS of Rats Subsequent to Administration of Opiates and their Antagonists".

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TELEPHONE
April 1, 1975 - March 31, 1977	$48,300.	392-3019

FIELD OF RESEARCH — SUJET DE LA RECHERCHE

[ ] EVALUATION — ÉVALUATION [X] BIOMEDICAL — BIOMEDICALE [ ] BEHAVIORAL — COMPORTEMENT [ ] SOCIAL SCIENCE — SCIENCES SOCIALES [ ] MULTIDISCIPLINARY — MULTI DISCIPLINAIRE

We have observed that when rats were treated with heroin (7.5 mg/kg) and brain synaptosomes harvested 0.5 h post-drug treatment, there was in addition to an increase in synaptosomal ACh, a decrease in the fluorescence produced on interaction of ANS with the synaptosomes. When such particles were harvested 48 h post-drug treatment, synaptosomes from heroin-treated rats showed a decrease in ACh content and an increase in ANS fluorescence. Synaptosomes harvested from animals killed during thebaine, picrotoxin or metrazole induced convulsions had normal ANS fluorescence. The ATP content of synaptosomes harvested either 0.5 h or 48 h after drug administration was increased by 10%. In addition, we have examined the possibility that opiate administration to rats might alter the activity of enzymes bound to the synaptosome membrane and found that the adenyl cyclase activity from rats killed 0.5 h after morphine administration is decreased by 60%, while its activity in synaptosomes harvested 48 h post-morphine showed an increase of 35%. In contrast the activity of acetylcholinesterase activity which is not bound to the synaptosomal membrane is virtually unaffected by the morphine treatment.

It was also observed that when rats were treated with heroin or morphine (25 mg/kg) there was at 0.5 h post-drug treatment a decrease in the permeability of brain mitochondria to phenazine methosulfate (PMS) and in the fluorescence produced on their interaction with ANS. When such particles were harvested 48 h post-drug treatment only mitochondria from heroin-treated rats showed an increase in permeability to PMS and in ANS fluorescence. Mitochondria harvested from animals killed during thebaine, picrotoxin or metrazole induced convulsions had normal ANS fluorescence. The respiration of brain mitochondria harvested 0.5 h after morphine administration to rats was decreased by 30%. As expected, the ATP content of these mitochondria was reduced by 10%. The inhibitory effect of morphine on respiration was abolished by lysis of the mitochondria with lysolecithin suggestive over decrease in membrane permeability. Mitochondria harvested 48 h post-morphine administration showed 10% increase in ATP content and in addition a 50% increase in respiration; lysis of such mitochondria further enhanced the respiratory activity by about 130% over the appropriate controls.

Since a decrease in ANS fluorescence in such membranes and proteins is indicative of a hydrophilic reaction while an increase is associated with a hydrophobic reaction and in addition, such changes are indicative of structural or conformational changes, we have examined the possibility of generating Arrhenius plots with two mitochondrial bound enzymes succin-oxidase and Mg^{2+} ATPase. In both instances it was observed that the treatment of the rat with morphine in vivo caused a decrease in the phase transition of the enzymes by about 2°. The effect was abolished when the animal was treated with BC 2605 A, 15 min after morphine administration. When Arrhenius plots were prepared from mitochondria harvested 48 h post-morphine administration, there was an increase in the phase transition temperature of both enzymes. These results provide support for our view that morphine and heroin administration to rats in vivo induce a structural alteration in the brain mitochondrial and synaptosomal membranes and further that this alteration affects the overall metabolic function of these organelles. In addition the effect obtained are entirely independent on the time of sampling.

Other investigators have shown that subsequent to the chronic administration of morphine to rats 48 h post-withdrawal of the drug there is a certain weight loss in these animals. We have observed that when rats have been treated chronically with morphine over a 7-day period with dosages of the drug which are known to produce tolerance and dependence, 48 h after withdrawal of the drug there was a significant weight loss in the animals. In addition there was a significant fall in rectal temperature during the withdrawal phase. Biochemical analyses of blood from these animals during withdrawal indicated that the SGOT, LDH, CPK and creatinine in the serum and urine were variable throughout the 4-week period of the experiment. However, the serum levels of triglycerides, urea nitrogen and uric acid during the withdrawal phase showed significant increases above the control. These increases were 53, 62 and 21% respectively over the control values. From these results we conclude that the weight lost 48 h following withdrawal from opiate administration is due to a drastic increase in the metabolism of carbohydrate, protein and nucleic acids since the animals did not excrete an abnormal amount of urine while they continued to eat normally, if not more. This overall effect would reduce the muscle mass of the rat and contribute most of the weight loss.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
G.E. Johnson

DEPARTMENT – DÉPARTEMENT
Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Saskatchewan, Saskatoon, Canada S7N OWO.

PROJECT TITLE – TITRE DU PROJET
The Influence of Chronic Ethanol Consumption on Drug Absorption, Distribution and Elimination.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
		306-343-2614

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
☐ EVALUATION – ÉVALUATION ☒ BIOMEDICAL – BIOMEDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Male Wistar rats, 250-275 gms were fed a diet containing ethanol (8.5% v/v) in metrecal for 14 days. The quantity of the diet consumed daily was measured and provided 4-8 gms of ethanol daily. This diet provided 35% of the calories from its ethanol component. Control rats received the metrecal diet in which the ethanol was replaced by an equal caloric amount of sucrose. After 14 days on the ethanol treatment, the rats were administered the control diet for one day. On day 16 both groups of rats were administered ^{35}S-chlorpromazine orally, intraperitoneally or intravenously. The levels of radioactivity in blood, bile, tissues, feces and urine were measured in both groups of rats. In addition, an inverse isotope solution analysis was established to measure unchanged radioactive chlorpromazine. Results of the study demonstrate that biliary excretion represents a major route for the elimination of chlorpromazine metabolites from the circulation of the rat. Extensive tissue binding of the drug was also found. No effect of ethanol pretreatment was seen on the absorption, distribution and rate of elimination of chlorpromazine. Furthermore, chronic ethanol pretreatment did not appear to influence the metabolism of chlorpromazine. Additional studies have been performed with the antiepileptic combination diphenylhydantoin and phenobarbital. Chronic administration of ethanol for 14 days followed by one day ethanol free did not influence the absorption, distribution and rate of elimination of diphenylhydantoin or phenobarbital.

These results differ from those obtained earlier with thiopental (1). Chronic ethanol administration for 14 days was seen to lower the serum level of thiopental and increase its uptake by the liver during the first minute after i.v. administration.

Results published in 1975 by Sellmann et al (2,3) have suggested that chronic ethanol administration to rats and humans lowers the serum level of intravenously administered diazepam. Studies are in progress to confirm these results and to determine the alterations in tissue uptake of diazepam in the ethanol pretreated rats. Studies of this nature have considerable significance with respect to the non-medical use of drugs such as ethanol. If it can be demonstrated that a significant number of drugs undergo altered absorption, distribution or elimination as a result of chronic ethanol consumption, then the pharmacological consequences of chronic alcohol use will become more apparent to the lay public. Furthermore, physicians will be placed in a better position with respect to judging drug dosages when treating alcoholic subjects.

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(2) Sellmann, R., Pekkarinen, A., Kangas, L. and Raijola, E. Acta pharmacol. toxicol. 36, 25-32, 1975.

(3) Sellmann, R., Kanto, J., Raijola, E. and Pekkarinen, A. Acta pharmacol. toxicol. 36, 33-38, 1975.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
K. Krnjević & O. Calvillo	ANAESTHESIA RESEARCH

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
McGill University, McIntyre Medical Bldg., 3655 Drummond Street, Montreal

PROJECT TITLE — TITRE DU PROJET
Action of morphine on neurones and synaptic transmission in brain & spinal cord

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975-76	$30,469.	

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[ ] EVALUATION ÉVALUATION
[X] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This study (by Dr. Calvillo) was undertaken to examine the effects of narcotic analgesics and their antagonists on sensory transmission in the spinal cord of the cat, using a conventional neurophysiological preparation, i.e. decerebrate spinal cats or cats anaesthetized with chloralose (i.v.). The technique of microiontophoresis was used to study the effects of the narcotic analgesic on single nociceptive neurones. Drugs so applied depressed the neuronal discharges evoked by stimulating the skin with noxious heat and noxious mechanical stimulation; non-noxious responses such as hair and touch were not affected to a comparable degree - thus indicating some specificity of narcotics for nociceptive responses. These depressant effects were reversed by the narcotic antagonist naloxone applied by microiontophoresis or administered intravenously.

As the microiontophoretic application of drugs is highly artificial, it was of interest to compare these effects with those of intravenous administration. The results obtained were essentially the same, suggesting that a similar concentration of drug is achieved by both kinds of administration at the site of action, i.e. the receptor. As the depressant actions of the narcotics were reversible by naloxone, it is concluded that the effect was mediated by a specific opiate receptor. Sparing of non-nociceptive responses of neurones showing convergence of noxious and innocuous inputs could be explained by a presynaptic site of narcotic action. The effects of these drugs were tested on cutaneous receptors and the corresponding peripheral nerves. None of the drugs tested had any effect suggesting that these might be significant sites of action. Further presynaptic testing was done by stimulating the terminal, intraspinal portion of primary afferent fibres of cutaneous nerves. These drugs increased the terminal excitability, therefore indicating that they have a direct presynaptic depolarizing action that may explain their analgesic depressant effects. These studies are significant in that they help to understand the physiology and pharmacology of pain and may enhance our ability to deal with painful syndromes clinically.

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3. O.Calvillo, J.L. Henry and R.S. Neuman, 1974. Effects of morphine and naloxone on dorsal horn neurones in the cat. Can.J.Physiol.Pharmacol.52, 1207.
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Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Michael Mayersohn	Pharmacy

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Faculty of Pharmacy, University of Toronto, Toronto, Ontario M5S 1A1

PROJECT TITLE TITRE DU PROJET

The Disposition and Response Kinetics of Disulfiram in Dogs

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-76	$6,500.00	(416) 928-6483

FIELD OF RESEARCH SUJET DE LA RECHERCHE

[ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Description: The research program has been designed to examine the kinetics of disposition of disulfiram and its metabolite (diethyldithiocarbamate) in the dog. The time course of pharmacologic response of disulfiram and its metabolite in the presence of ethanol will be explored and the relationship between response and plasma drug levels will be examined. From these results and the development of a reasonable biologic model an implant dosage form of disulfiram will be designed and evaluated.

2. Key Findings: The major obstacle encountered in this work has been the development of specific, sensitive assays for disulfiram and its metabolite from plasma. Previously reported literature assays are both insensitive and non-specific. The lack of specificity prevents distinguishing between disulfiram and its metabolite. An additional problem is the poor stability of both chemical forms in aqueous fluids. A specific gas liquid chromatographic assay has been developed for the metabolite from plasma. Studies using atomic absorption and quantitative thin layer chromatography indicate that the metabolite exists partially as a metal complex in the plasma. Intravenous infusion studies in the dog indicate that metabolite disposition may be described by a two compartment pharmacokinetic model. The terminal half-life of the metabolite ($t_{\frac{1}{2}}.\beta$) is approximately 55 minutes indicating rapid elimination. The metabolite is readily metabolized in whole blood and appears to account for a substantial faction of total metabolism, the remainder most likely taking place in the liver.

3. Significance: The purpose of this project is to improve disulfiram therapy by providing fundamental information to make its use more rational. As we know essentially nothing about the quantitative disposition of the drug and its metabolite it is impossible to develop methods of therapy (e.g., implantation) that are anything but empirical. By obtaining some of this basic information about the disposition and response kinetics of the drug and its metabolite it is hoped that a more quantitative, exact approach may be taken. Furthermore, disulfiram has been implicated in numerous drug-drug interactions. The findings of this research may have some implications in explaining those interactions.

4. Future Research Directions: Presently studies are being done to completely characterize the disposition kinetics of disulfiram metabolite and the influence of ethanol on the disposition kinetics and response in the animal. A specific assay for disulfiram is being explored using several methods. Once this is accomplished disulfiram disposition kinetics will be explored along with the response to ethanol. Ultimately we hope to design an implant dosage form of disulfiram that will have the appropriate release patterns to maintain therapeutic disulfiram levels.

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NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
I.M. Mazurkiewicz-Kwilecki D.A.V. Peters	Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Faculty of Medicine, University of Ottawa, Ottawa, Ont.

PROJECT TITLE – TITRE DU PROJET

Pharmacological Studies on Mandrax and Methaqualone

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1973-74 - 1974-75	$42,813	231-4078

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

In recent years Methaqualone (MTQ) and more recently Mandrax (MA), a combination of MTQ with Diphenhydramine (DIPH) in a ratio 10:1, have become of special concern as another group of drugs abused by the young population. In spite of the seriousness of toxic effects induced by these drugs their pharmacological effects were little explored.

In our previous studies (1) chronic treatment with another drug of abuse, Δ^9-tetrahydrocannabinol, resulted in a significant increase in the synthesis of H^3-catecholamines in the brain and adrenals.

We also reported previously (2) significant changes in brain histamine concentration following chronic administration of other drugs of abuse such as narcotic analgesics.

It was therefore of interest to investigate the effects of MA and its components on the concentration and/or synthesis of these biogenic amines in different regions of the rat brain.

Present studies indicate (3) that acute oral treatment with MA or its active components, MTQ or DIPH, resulted in a decrease in the hypothalamic histamine concentration. The effects of MA and MTQ but not of DIPH were attenuated after chronic treatment with a steady dose of MA, but were noticeable again when MA was administered chronically in increasing doses. The observed changes were reversible after MA withdrawal. These alterations in brain histamine concentration were associated with an increase in histidine decarboxylase activity which is consistent with drug-induced alterations in histamine synthesis (4,5).

In addition, acute oral administration of MA (55 mg/kg) significantly increased (38%) incorporation of H^3-tyrosine into H^3-catecholamines in the pons-medulla region; an increase (20%) was also noted in the cortex and midbrain. Hypothalamic norepinephrine concentration was slightly lowered (13%) while no significant changes were noted in the

pons-medulla and midbrain. Dopamine concentration in the corpus striatum remained unchanged. High doses of MA (165 mg/kg) administered orally also influenced 5-hydroxytryptamine turnover in the rat brain. This work is being prepared for publication.

Acute oral administration of MA induced significant hypotensive effects and a significant decrease in the heart rate which seemed to be dose dependent. The mechanism of these changes is being explored. Chronic studies are also being carried out to test for any tolerance development to these effects.

The role of histamine in the mechanism of action of drugs of abuse was up to now little explored. Present studies indicate that in addition to other biogenic amines histamine, a putative neurotransmitter, may be involved in the mechanism of tolerance development and addiction to certain drugs. These observations may open new vistas for a possible role of histamine in the pharmacological effects of drugs of abuse.

It is pertinent to investigate drugs which could prevent or reverse the observed biochemical changes. Such drugs could find some important clinical application and reduce problems associated with non-medical use of drugs.

Key words

Mandrax	Diphenhydramine	Brain catecholamines	Norepinephrine
Methaqualone	Histamine	Drugs of abuse	5-Hydroxytryptamine

Publications

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5. I.M. Mazurkiewicz-Kwilecki and B. Bielkiewicz Brain Histidine decarboxylase activity after acute and chronic administration of Mandrax, in preparation for publication.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
P.L. McGeer	Dept. of Psychiatry Div. of Neurological Sciences
INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE	The University of British Columbia, Faculty of Medicine, Kinsmen Laboratory of Neurological Research, Vanc., B. C.
PROJECT TITLE – TITRE DU PROJET	Possible structural and biochemical alterations in brain tissue following Δ^9-THC administration.
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	1975-1976
FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	$47,050
TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE	(604) 228-2481

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☒ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This research was aimed at assessing the effects of cannabinoids on the essential metabolism of brain and other tissues. Significant inhibition of protein and nucleic synthesis has been demonstrated in both brain and testis:

1) A study was undertaken to examine the distribution and binding of ^{3}H-Δ^8-THC in the subcellular compounds of the brain, liver and kidney after i.v. administration to rats (nuclei, mitochondria, microsomes and soluble).

   The amount bound and the subcellular distribution varied from tissue to tissue suggesting that differential subcellular distribution and binding of THC and/or metabolites may be of importance in determining the physiological and pharmacological effects of THC.

   (A. Jakubovic, P. L. McGeer: Res. Communication Chem. Pathol. Pharmacol. 9, 197 (1974)

2) Several reports suggested a possible teratogenic effect for marijuana or Δ^9-THC. We have studied the effect of Δ^9-THC and/or alcohol on the developing chick-embryo. With repetitive injections the body weight of the chick embryo was reduced, the liver weight increased and the weight of the forebrain decreased. Apparent changes were found in the specific activities of protein and nucleic acid synthesized from injected radioactive precursors in different parts of the brain and liver. No visible teratogenic effects were noted with the dosage schedules used.

   (A. Jakubovic, P. L. McGeer and R. C. Fitzsimons: J. Toxicol. Environmental Health - in press)

3) Different cannabinoids were studied for their effect on protein, nucleic and lipid synthesis, as well as other metabolic processes in rat testis tissues. The metabolism was measured in vitro so that direct effects could be observed in the absence of complicating in vivo hormonal interrelationships.

   The results show that psychogenically active, less active or inactive cannabinoids all brought about significant changes in biosynthesis of protein, ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and lipids in the rat testis. These results compare with those previously obtained with THC in brain tissues.

   (A. Jakubovic, P. L. McGeer: Can. J. Biochem. 50, 654 (1972).

Project title: Possible structural and biochemical alterations in brain tissue following Δ^9-THC administration.

The diminished biosynthesis of RNA and DNA appears to be related to the inhibition of essential phosphorylation steps of the nucleic acid precursors. The inhibition of protein synthesis may be a result of decreased nucleic acid levels, and/or decreased energy levels in the cells.

The present results may help to explain the decreased spermatogenesis and some other effects on gonadal functions in cannabis users. Furthermore, they indicate that a cautious attitude should be taken regarding the potential effects of cannabis derivatives, and much closer scrutiny made of the particular contribution of the psychogenically inactive cannabinoids to the overall effects of such preparations as marijuana and hashish.

(Jakubovic, A., and McGeer, P. L., In Vitro Inhibition of Protein and Nucleic Acid Synthesis and Rat Testicular Tissue by Cannabinoids. Paper presented at the Satellite Symposium on Marijuana. Sixth International Congress of Pharmacology, July 26-27, 1975, Helsinki. In press.)

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
NOSAL GILLIANE G.-Nosal	Pharmacologie, Faculté de Médecine
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE: Université Laval, Québec G1K 7P4, Canada	
PROJECT TITLE – TITRE DU PROJET: Consequences of maternal narcotic dependence of the infant animal. Short-term effects	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES: 1976 et 1977	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES:
TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE:	

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION – ÉVALUATION ☒ BIOMEDICAL – BIOMEDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Brève description du projet et résultats préliminaires

Ce projet a pour objectif principal, l'étude des conséquences pour la descendance de la dépendance maternelle aux Narcotiques (Morphine, en expérimentation animale). Celui-ci devrait se réaliser en deux étapes :

I. ETUDE DES EFFETS A COURT-TERME dans la période postnatale précoce du développement (projet actuel) comportant :

1. l'induction expérimentale de la dépendance à la Morphine (passive par injection forcée suivie de l'induction active par auto-administration) chez la femelle avant la fécondation et maintenue tout au long de la gestation.

2. l'établissement d'un modèle animal des effets sélectifs de la dépendance maternelle, à la naissance et au cours de l'enfance précoce :

   - Syndrome d'Abstinence Néonatale (SAN)
   - autres conséquences immédiates de la morphine ante-natale sur la maturation cérébrale et l'évolution neuro-comportementale du raton

Ce modèle comporte l'établissement de critères spécifiques comportementaux et neuronaux, caractéristiques de l'exposition in utero aux Narcotiques sur la descendance.

II. ETUDE DES EFFETS A PLUS LONG TERME (orientation future et extension du projet actuel) qui a pour but d'explorer les séquelles prolongées sur le comportement de l'animal, jeune et adulte, principalement l'identification des défauts de réactions comportementales (activité réflexe, réponses sensorielles et motrices, apprentissage, mémoire), les possibilités de vieillissement cérébral précoce et la présomption à établir d'une prédisposition marquée à un passage de la dépendance physique passivement acquise in utero, à une toxicomanie active aux Narcotiques au cours de l'adolescence et/ou de la maturité.

Globalement, cette recherche a été conçue pour finalement déboucher sur l'exploration documentée et rationnelle des moyens de prévention et de traitement :

- d'une part, du Syndrome d'Abstinence Néonatale (état de détresse du nouveau-né par sevrage de la drogue maternelle à la naissance);
- d'autre part, des autres effets possibles induits à brève échéance par l'exposition intra-utérine à la Morphine.

Cette partie de la recherche inclura également l'évaluation du traitement symptomatique du SAN, en usage clinique actuellement, quant à son efficacité pour le réduire ou le contrecarrer (Barbituriques et Tranquillisants) de même que leurs effets propres possibles sur l'évolution neuro-comportementale ultérieure du bébé.

La recherche en étant à ses débuts, les données obtenues à date portent essentiellement sur la résolution de certains problèmes expérimentaux :
(1) conditions optimales, biologiques et d'environnement, en vue d'assurer la réussite de la fécondation (fertilité parentale, cycle oestral, fécondation naturelle et insémination artificielle), de la gestation (évolution pondérale, alimentation maternelle) et de la mise bas (cages de maternité, cf. publication);

(2) induction expérimentale de la dépendance maternelle à la Morphine :

- administration initiale forcée (détermination des doses et du rythme d'administration)
- auto-administration orale (conditions d'entretien de la dépendance : enregistrement de la fréquence et de la durée des prises);
- essais de plusieurs composés en vue d'éviter le phénomène aversif de l'animal en face de l'amertume de la Morphine (sucrose, saccharine et quinine).

(3) standardisation des critères sélectifs de la maturation cérébrale en termes de neuronogénèse (cf. publications) et de l'évolution neuro-comportementale (cf. publications) du raton normal.

(4) données préliminaires sur les effets à court- terme de l'exposition foetale à la Morphine: anomalies néonatales, refus de maternage et mise en nourrice, difficultés d'alimentation et de croissance néonatales, présomptions à confirmer concernant l'interférence possible de la drogue maternelle sur le développement foetal : neuronogénèse morphologique modifiée de la cellule de Purkinje (système intraneuronal de synthèse protéique) et évolution neuro-comportementale altérée (réflexes, réactions motrices).

Importance du projet et contributions attendues

Les bénéfices attendus de cette recherche reposent sur la possibilité d'une contribution en expérimentation animale :

1. A une meilleure connaissance et à une caractérisation précise des effets à court terme :
   - le Syndrome d'Abstinence Néonatale aux Narcotiques (dont l'occurrence serait de 2/3 enfants nés de mères héroïnomanes): identification des symptômes, évaluation de la gravité de chacun des signes et du syndrome global);
   - l'interférence susceptée de la drogue maternelle sur la croissance embryo-foetale et sur le développement et la maturation cérébrale ultérieurs de l'enfant;
2. A une exploration prévisionnelle des conséquences à une plus longue échéance, au cours de l'enfance et de l'adolescence, de l'exposition intrautérine à la drogue :
   - sur l'évolution neuro-comportementale (capacités sensorio-motrices, coordination motrice et habileté fondamentale, performances physiques et intellectuelles, apprentissage, mémoire et maturation affective);
   - sur l'interférence prolongée de la drogue avec la maturation postnatale du cerveau: altérations neuro-chimiques et fonctionnelles acquises in utero et qui seraient susceptibles de conduire : d'une part, à un vieillissement cérébral précoce et d'autre part à une prédisposition marquée à un passage, au cours de l'adolescence et/ou de l'état adulte, à une toxicomanie active.
3. A une approche rationnelle au traitement et à la prévention de ces effets : SAN et autres effets à court et à long termes (extension de la recherche actuelle) :
   - validité des mesures palliatives, utilisées en pratique clinique pour contrecarrer le SAN. Efficacité thérapeutique des Barbituriques et des Tranquillisants majeurs (Chlorpromazine) et exploration des effets propres de ces médicaments sur l'évolution postnatale de l'enfant;
- approche à des moyens de préventions du SAN, si possible, de l'interférence de la drogue avec le développement physique et mental du bébé;
- mesures préventives pour tenter d'éviter le passage possible à la toxicomanie active du sujet rendu dépendant passivement au cours de sa vie foetale.

En d'autres termes, l'objectif de la recherche est de contribuer à une connaissance plus précise et mieux documentée des répercussions de la toxicomanie maternelle en vue d'améliorer l'avenir de l'enfant et, si possible, de lui éviter les conséquences à plus ou moins longue échéance de son exposition intrautérine aux drogues.

1. Nosal, Gilliane, Lin, K.N. et Lapointe, G.

Un modèle neuronal pour recherches cytopharmacologiques sur l'animal en développement

Ann. ACFAS, 1975, 42 (1) : 110

2. Lapointe, G., Lin, K.N. et Nosal, Gilliane

Un modèle neuro-comportemental pour recherches pharmacologiques sur l'animal en développement

Ann. ACFAS, 1975, 42 (1) : 110

3. Nosal, Gilliane, Lin, K.N. and Lapointe, G.

Neuronogenesis in developing animal as a neuronal model for cytopharmacological investigations

Proc. Can. Fed. Biol. Soc., 1975, 18: 108 (430)

4. Lapointe, G., Lin, K.N. and Nosal, Gilliane

Neuro-behavioral model for pharmacological researches on developing small rodents

Proc. Can. Fed. Biol. Soc., 1975, 18: 108 (429)

5. Nosal, Gilliane, Lapointe, G. et Lin, K.N.

Etude ultrastructurale sur la maturation neuronale chez les petits rongeurs

C.R. Soc. Microsc. Can., 1975, 2: 98

6. Lapointe, G. et Nosal, Gilliane

Unité de cages de maternité pour recherches sur le développement du rat

Vie Méd. Can. Franç., 1975, 4 (9) : 1111

7. Nosal, Gilliane (dans)

La Drogue ou la Vie

Québec Science, 1975, 14 (3) : 9

8. Nosal, Gilliane, Lin, K.N. et Lapointe, G.

Maturation néo- et post-natale dans le cortex cérébelleux de la souris. Etude ultrastructurale

Acta Neurol. Latinoamer., 1975 (sous presse)

9. Nosal, Gilliane, Lapointe, G., Lin, K.N. and Radouco-Thomas, C.

Short-term effects of in utero induced Morphine dependence in the infant rat

Proc. VI th Intern. Congress Pharmacology (Helsinki) 1975, 429 (1010)

10. Nosal, Gilliane

Drogues et maternité : un dilemme pour la femme? Données actuelles et perspectives

Toxicomanies, 1976 (sous presse)

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
JOHN P.J. PINEL	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B.C. V6T 1W5

PROJECT TITLE – TITRE DU PROJET
Repeated administration of convulsive agents and the alcohol withdrawal syndrome

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-77	$44,000	(604) 228-4656

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Periodic bipolar stimulation of any of a number of sites throughout the brain can lead to the gradual development and intensification of behavioral convulsions (kindling) in a variety of species (Goddard, McIntyre & Leech, 1969), even at current intensities initially too low to produce any behavioral or electrographic effects. For example, if the rat amygdala is periodically stimulated at a level which produces neither electrographic nor behavioral effects, eventually the afterdischarge threshold may be reduced to the point that subsequent stimulations reliably elicit afterdischarges. If stimulations are then continued, mild motor automatisms may appear which increase in severity with each successive stimulation until motor seizures, characterized by facial and forelimb clonus, rearing, and a loss of equilibrium can be reliably elicited (Racine, 1972a).

One of the major features of this kindling phenomenon is its generality; similar effects have been demonstrated with a variety of potentially convulsive agents including electroconvulsive shock (ECS). Ramer and Pinel (in press) found that ECSs administered to experimental animals at 3-day intervals produced motor seizures of gradually increasing severity. Another major characteristic of kindling is that the increase in seizure susceptibility is not limited to the agents that initially produced the kindling. Animals kindled with local amygdaloid stimulation have been shown to be more susceptible to seizures induced by metrazol (Pinel, Mucha & Skelton, 1975) and those receiving periodic ECSs have been found to be more susceptible to fluorothyl-induced seizures (Prichard, Gallagher & Glaser, 1969).

In view of this kindling literature, we have been testing the hypothesis that electroconvulsive therapy might produce an enduring increase in the susceptibility to seizures induced by alcohol withdrawal. In most of our studies experimental rats have received a series of 10 ECSs administered at 3-day intervals, followed by intubation with intoxicating doses of alcohol three times per day for 15 days. The incidence of various convulsive responses was assessed by a "blind" observer during thewithdrawal period.

We have consistently found that the ECS-produced motor seizures progressively increase in severity and that the animals receiving the ECSs eventually display a severe alcohol withdrawal syndrome. This increased susceptibility to alcohol withdrawal lasts for several weeks following the tenth ECS and neither the kindling nor the increased susceptibilty to alcohol withdrawal seizures occurs when ECSs are administered at intervals of less than one day.

Although such laboratory studies do not prove that such kindling effects do result from the clinical application of convulsive therapies, our results have indicated that this is not unlikely. Thus, until the appropriate clinical tests have been performed, drug intake following repeated convulsive treatments should be carefully controlled.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
R.E. Rangno, M.D.	Pharmacology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
McGill University

PROJECT TITLE — TITRE DU PROJET
Non-Medical Use of Drugs in Suicidal Overdose: Research into Some Problems

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
[ ] EVALUATION — ÉVALUATION
[X] BIOMEDICAL — BIOMÉDICALE
[ ] BEHAVIORAL — COMPORTEMENT
[ ] SOCIAL SCIENCE — SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

1. Brief Description of Research Project: One aspect of drug abuse which is a major public health problem but which has had insufficient, integrated, in depth research, is drug overdose. A retrolective prospective audit of this problem by our group has identified three priorities to which we propose a strategy of investigation. (1) The effect of severe drug overdose on cardiovascular function and the effect of correcting these abnormalities on drug disposition and the clinical course. Hypotension secondary to decreased cardiac output should be corrected rapidly and specifically to enhance hepatic and renal clearance of drugs. Throughout the patients treatment course, using relatively non-invasive techniques, we will study caridac output as a function of cardiac inotropy and venous return; the latter as influenced by blood volume and venous compliance. A smaller, more detailed study will assess hepatic clearance of drugs as a function of liver blood flow. (2) The effect of ethanol interaction with commonly used drugs on the kinetic disposition of the drugs and the clinical course. We plan a detailed pharmacokinetic analysis of the interaction of ethanol with common drugs in volunteers and in patients with severe drug-ethanol overdose to establish the mechanism of this life-threatening potentiation phenomenon. (3) The effect of gastric instillation of large amounts of activated charcoal on drug absorption and the clinical course. We believe our empiric use of activated charcoal decreases drug absorption and thereby lessens the severity and duration of the overdose state. We plan to lend fact to anecdote by comparing the patients course and the clearance of the drugs after double-blind treatment with either activated charcoal or inactive charcoal. The information from these three studies will be inter-related and new treatment methods devised and implemented. The impact of these innovations will be assessed by a continuing prospective audit. The results of that audit will be used to educate the medical community.

2. Summary of Key Findings: Part I of the above proposal is underway Part II and III are complete with the following initial observations.

Part II - The interaction of ethanol on the pharmacokinetic disposition of diazepam and amobarbital has been studied in a group of 16 normal volunteers. The data from this study is presently being subjected to computer kinetic analysis. We have also completed the analysis of ethanol use in patients with suicidal overdose with common drugs. About 50% of all overdose patients (n = 343) have measurable ethanol on arrival at hospital however of those patients with an overdose severe enough to require admission there is a significantly lesser incidence (34%) of ethanol consumption. Patients not requiring admission had a mean serum ethanol concentration of 1.78 gm/L. Of 24 patients requiring admission 17 were ethanol positive and these were in coma for a mean duration of 9.7 hours while 23 of 49 ethanol negative patients were in coma with a paradoxically greater mean duration of coma of 28.3 hours. Thus the combined ingestion of ethanol with an overdose of drug did not, contrary to expected, prolong coma. An explanation for the paradox was not in the type of drugs taken but probably in the amount ingested since those patients who did not ingest ethanol appeared to be more intent on successful suicide while the ethanol ingestors were usually suicide gestures. This was confirmed by there being significantly more patients admitted who had a history of previous overdose and were ethanol negative. We conclude that although ethanol might be expected to potentiate the severity of a drug overdose in actual

fact patients who ingest ethanol with their drug overdose most frequently have a much shorter duration of coma. This is probably because the amount of drug they ingest is much less than in those patients who do not ingest ethanol. The reasons for, and intent on, successful suicide appears to be different in these two seemingly distinct groups of patients. An abstract of the data on ethanol has been submitted to the Canadian Pharmacologic Society for presentation at the June/76 meeting of the Canadian Federation of Biological Societies. (attached)

Part III - The study of the efficacy of activated charcoal in drug overdose is near completion and some rather unexpected results have appeared. It had previously been shown that oral administration of activated charcoal decreased the absorption of therapeutic doses of some common drugs in man. In addition, oral activated charcoal in animal experimental overdose of common drugs substantially decreased the severity of the intoxication. We had been empirically instilling 100 gm of activated charcoal after gastric lavage in overdose patients for about 5 years prior to this study which started in February 1975. An audit of our experience during this empiric use of charcoal showed that more than 75% of all patients in coma were awake in less than 12 hours. We thought one explanation was that charcoal had decreased the absorption of drug. However, we considered other explanations such as aggressive conservative support of vital functions or simply a change in the epidemiology of drug use to compounds which produced a shorter coma. In our present study alternate overdose patients received either 100 gm of activated charcoal or a similar volume of water. We found that the charcoal-treated patients had no less chance of requiring admission for progression of the overdose. Similarly we found that in those patients admitted in coma, those who received charcoal had no difference in the duration of coma compared to those who had received water only. Once again, however, we showed that the duration of coma was very short in all patients i.e., 75% awoke in 12 hrs and 90% awoke in 24 hrs. Thus for a number of possible reasons the routine use of charcoal after gastric lavage does not appear warranted.

3. Significance of Project: The data from the project to date has been enlightening in 2 major aspects. First, the common belief that ethanol enhances the severity of suicidal overdose appears incorrect because the group of patients who ingest ethanol with their drugs probably ingest less drug. Second, the common recommendation for routine use of activated charcoal in drug overdose is not substantiated in this first controlled drug overdose study in man. The very short duration of coma in our experience could be secondary to aggressive care of vital functions, in particular hemodynamics and especially liver blood flow. Studies of the influence of liver blood flow on the clearance of common drugs are in progress.

4. Findings Relevant to Reducing Problems Associated with Non-Medical Drug Use: Our findings to date shed new light on our understanding of the very common social problem of drug abuse in suicidal overdose. Those patients who do ingest ethanol with their drugs are a distinct group and the interaction between ethanol and the drug does not appear to have clinical significance. Our findings also seem to settle the question of usefulness of activated charcoal in the extremely common problem of adult suicidal drug overdose. This form of almost standard treatment appears unwarranted and in fact may delay the more important aspect of treatment namely aggressive maintenance of vital functions. We do not see any immediate answer to the problem of patients demanding and physicians liberally prescribing drugs. There is definitely an inverse relationship between the affluence of our society and our tolerance to minor discomforts. We suggest that aggressive advertising to the public and physician plays a large role.

5. Future Directions of Research Projects: We believe that advances in the treatment of accidental and suicidal drug overdose lay in two areas. First it is known that most drugs are "eliminated" from the body by hepatic degradation. It has been shown that the clearance of some drugs is very dependent on liver blood flow. The importance of liver blood flow on the clearance of drugs commonly used in drug overdose has not been studied. Liver blood flow may be reduced in overdose states and should be able to be increased to normal or greater than normal. This is one of the few physiologic factors which can be manipulated since hepatic enzyme induction is not practical as a means of enhancing drug elimination. It is time we applied the same approach in manipulating hepatic physiology as we have with enhancing renal clearance of drugs. We also plan studies with 2 commercial hemoperfusion

devices available for clinical investigation. These consist of pumping blood directly over an activated charcoal matrix. Early studies in humans have shown them to be safe and very efficient. Further studies with charcoal hemoperfusion are required in patients in severe coma from different drugs. This non-specific treatment method could prove useful in the management of severe overdose in children and adults.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. V. Snieckus and Dr. J.G. Smith	Chemistry

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Waterloo, Department of Chemistry, Waterloo, Ontario

PROJECT TITLE – TITRE DU PROJET
Synthesis of Radiolabelled Tetrahydrocannabinol Derivatives.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974/1975	$10,000.00	(519) 885-1211

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [ ] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Description of Research Project

Our general research objective is to develop and refine synthetic routes to tetrahydrocannabinol (THC) derivatives which contains either tritium or carbon-14 radiolabels at selected sites in the molecule. Several syntheses are being explored and these are briefly described below:

(a) acid-catalyzed exchange of the aromatic ring protons of THC with tritium oxide. This procedure is considered satisfactory as completed and sample of labelled material are available on demand.

(b) synthesis of 11-^{14}C-Δ^9-THC from the readily available 11-norketohexahydrocannabinol-1-methyl ether.

(c) synthesis of olivetol (and hence Δ^9-THC) with a ^{14}C label in the pentyl side chain.

(d) development of a synthetic route to THC in which the radiolabelled methyl groups are attached to the C-6 carbon of the heterocyclic ring. These positions are metabolically inactive and thus the THC radiolabelled in this manner should be particularly valuable in metabolic studies.

Key Findings

We have been able to achieve workable syntheses of both Δ^8-THC and Δ^9-THC giving these cannabinoids in good yield and high optical purity. With these synthetic materials in hand, we have carried out 1) tritiation studies of THC and 2) exploratory work for the purpose of ^{14}C-labelling of certain THC derivatives.

As a prelude to the tritiation studies, we investigated the incorporation of deuterium (^{2}H) into Δ^9-THC under acid-catalyzed conditions (D_2O, D_3PO_4 in tetrahydrofuran, 80°C, 2 hr). This study showed that the C-2 proton undergoes exchange at a much faster rate than the C-4 proton. A 1-phosphate intermediate may be proposed to explain the rate difference in positional deuteration.

Using the acid catalyzed conditions described above, tritiation of Δ^9-THC has been accomplished, giving 50 mg quantities of ^{3}H-Δ^9-THC in greater than 90% purity and activity of approximately 20 C/mole. Methods to improve the efficiency of this synthesis e.g. by recovery of "spent" ^3H_2O are being investigated.

Significance of Project

Radiolabelled THC derivatives are required for biochemical and pharmacological studies for convenient and rapid detection of THC and its metabolic products. Such studies using radiolabelled THC increase our understanding of the manner in which marihuana affects the body and assist the development of analytical techniques for detecting THC and its metabolites in body fluids.

Findings Relevant to Reducing Problems Associated with Non-Medical Drug Use

The biologically active constituents of Cannabis sativa have aroused much public and scientific interest and the physiological and psycholgoical effects of marijuana are of considerable contemporary concern. Much has been learned of the metabolism in vitro of the important cannabinoids but in vivo metabolic studies remain both challenging and pertinent.

Of invaluable assistance in such studies is the use of tetrahydrocannabinol or related cannabinoids containing radiolabels in appropriate portions of the molecule. Such compounds permit easy detection and hence isolation of the metabolites which contain the radioactive label. A major difficulty with previous radiolabelled preparations is the partial loss of radioactivity during metabolism. Therefore it is important to synthesize compounds with radiolabels at positions which are metabolically inactive.

It is the purpose of the proposed research to develop synthetic routes to tetrahydrocannabinol and related compounds which are labelled with tritium or with carbon-14 at specific and largely metabolically unaffected molecular sites. With the synthetic means on hand, we shall be in a position to supply such materials to those research groups interested in metabolic studies.

Future Directions of Research Projects

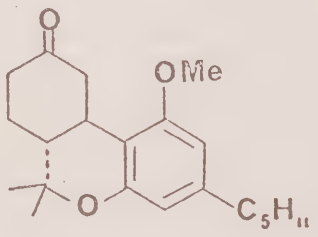
We have recently prepared and made available tritiated Δ^9-THC. The objective of our present proposal is to develop simple and convenient syntheses of chiral (optically active), specifically ^{14}C-labelled THC derivatives. As a result of this study compounds would be available which would not suffer loss of radiolabel in metabolism and would therefore be invaluable aids in biochemical investigations.

Our specific objectives are as follows:

(a) synthesis of chiral 11-^{14}C-Δ^9-THC using the readily available 11-Norketohexahydrocannabinol-1-methyl ether (2) ;

(b) syntheses of olivetol (7) and chiral lactone 13 which would be amenable to the introduction of ^{14}C-label in the C_5-side chain of 7 and C_6-position of 2 respectively;

(c) execution of the radiolabelling as indicated in (b).



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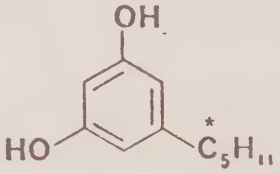

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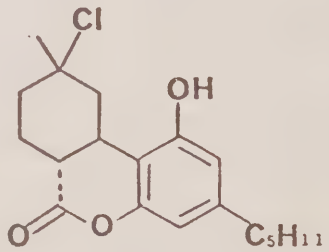

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Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. Roger Stretch	Psychology and Pharmacology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Ottawa, 1245 Kilborn Ave., Ottawa, Ontario K1N 6N5

PROJECT TITLE TITRE DU PROJET Experimental investigations of behavioural and pharmacological determinants of drug dependence in monkeys.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TELEPHONE
1973-1977	1976-77: $92,750.00	231-7012

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMÉDICALE [X] BEHAVIORAL COMPORTEMENT [ ] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

DESCRIPTION OF RESEARCH PROJECT AND CURRENT EXPERIMENTS

1. SCHEDULE CONTROL OF DRUG-SEEKING BEHAVIOUR IN MONKEYS

In the analysis of drug-seeking behaviour in animals, experimental conditions are so arranged that a behavioural response is followed by prompt administration of the drug. If the response increases in frequency then the drug is defined as a positive reinforcer for the behaviour leading to its administration.[1] Many psychoactive drugs are known to serve as positive reinforcers in animals; results have generally shown that drugs which act in this manner in infra-human primates are those that induce dependence in man. Although several routes of administration have been employed in drug reinforcement experiments, the most commonly-used for water-soluble compounds is by intravenous injection.

(a) Intravenous drug injections as events that control operant behaviour in monkeys: Several series of experiments are being undertaken to analyse the relative reinforcing effects of dependence-producing drugs in monkeys using a chronic i.v. catheterization technique.[2] Recent work[3,4,5] has been concerned chiefly with discriminative control of i.v. amphetamine or cocaine self-injection behaviours under modified progressive ratio schedules of drug reinforcement. For example[5], responding was stabilized in monkeys under a modified progressive-ratio schedule of i.v. d-amphetamine or cocaine self-administration. Substitution of saline for the drug solution resulted in rapid extinction of self-injection behaviour; i.v. injection of certain doses of d-amphetamine or cocaine prior to test sessions in which response-dependent saline infusions were available, reinstated the rate and patterning of responding observed during previous sessions in which drug solutions were available for self-injection. Presession i.v. injections of several doses of pentobarbital or chlorpromazine failed to consistently reinstate responding. Results were interpreted in terms of the discriminative control of drug self-injection behaviours by the current drug state of the monkey.

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1 For a review of drug self-administration methodology, see Evaluation of Dependence Liability and Dependence Potential of Drugs. Tech. Report Series #577, World Health Organization, Geneva, 1975.

2 Stretch, R. and Gerber, G.J., 1970. Can. J. Physiol. Pharmacol. 48, 575-581.

3 Stretch, R. et al., 1971. Can. J. Physiol. Pharmacol. 49, 581-589.

4 Stretch, R. and Gerber, G.J. 1973 Can. J. Psychol. 27, 168-177.

5 Gerber, G.J. and Stretch, R. 1975. Pharmacol. Biochem. Behav. 3, 1055-1061.

Experiments have also been completed[6] dealing with cocaine self-injection behaviour under schedules of delayed reinforcement. Rates of lever pressing maintained either by response-dependent i.v. injections of cocaine (250 mcg/kg/inj.) or by food-pellet presentation were compared and found to vary systematically as a function of the delay (5-100 sec) imposed between response(s) and the delivery of each injection. The control of responding by two schedules of delayed reinforcement was studied. The first schedule (Type Nl Tx sec) permitted responses to occur during the delay period without any programmed consequence; the second schedule (Type Nl Tx sec) required a response, and then the elapse of x sec without any additional response(s). At imposed delays of 50 and 100 sec, response rates were reduced significantly when the second schedule was in effect by comparison with the first. The effect was observed when responding was maintained either by i.v. cocaine injections or by food-pellet presentation. Across all comparable delay conditions, response rates were higher when maintained by cocaine injections than by food-pellets. Rate-enhancement generally induced by drugs of the psychomotor stimulant type[7] can account for the observed difference.

(b) Discrete-trial schedules of i.v. drug reinforcement: cocaine and morphine: Since free-operant schedules rely on rate measures, they are not necessarily optimal to assess some behavioural effects of drugs. In discrete-trial procedures, an exteroceptive signal is presented at a time controlled by the experimenter and a single response during the signal is required for presentation of the reinforcer. The measure of responding is a probability, i.e. the proportion of the stimulus occasions on which the designated operant occurs, rather than response-rate. Employing a discrete-trials procedure, the following experiments have been completed or are in progress:

(i) Cocaine self-administration during daily sessions consisting of 40 discrete-trials at an inter-trial interval of 50 sec, cross-substituting saline and each of the following unit injection doses for a minimum of 5 consecutive sessions: 25, 50, 100, 200, 300 and 400 mcg/kg/inj. Results show that the proportion of trials on which cocaine is self-injected increases up to 100 mcg/kg/inj; response-probability then decreases in a dose-dependent manner at unit injection doses exceeding 100 mcg/kg/inj. In additional experiments, the effects of (presession) i.m. injections of chlorpromazine, chlordiazepoxide and haloperidol upon cocaine self-injection behaviour are being determined.

(ii) Morphine self-administration during daily sessions consisting of 40 discrete-trials at an inter-trial interval of 50 sec, substituting saline and each of the following unit injection doses for a minimum of 5 consecutive sessions: 10, 25, 50, 100, 200, 300 and 400 mcg/kg/inj. As the injection dose is increased, response-probability increases, then decreases; the maximal response-probabilities were observed at unit injection doses of 25 and 50 mcg/kg/inj. In subsidiary experiments, the effects of (presession) i.m. injections of chlorpromazine, haloperidol and morphine are being assessed in addition to pretreatment by drugs with antagonist (naloxone) or mixed agonist-antagonist properties (e.g., nalorphine, pentazocine and cyclazocine).

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6 Stretch, R. et al. 1976 Can. J. Physiol. Pharmacol. (submitted mss).

7 For example: Stretch, R. and Skinner, N. 1969. Psychopharmacologia, 16, 89-104; Dalrymple, S.D. and Stretch, R., 1971. Psychopharmacologi 21, 268-282; Orloff, E.R. and Stretch, R., 1975. Psychopharmacologia, 45, 29-37.

(iii) Morphine self-administration by monkeys during daily sessions consisting of 40 discrete-trials at inter-trial intervals of 50, 150 and 300 sec, also varying unit injection dose across the range 25-400 mcg/kg/inj. Results show that response-probability remains primarily a function of unit injection dose despite variation of the inter-trial interval, i.e., response-probability associated with a given unit injection dose remains unaffected at an imposed inter-trial interval of 300 sec.

(iv) Morphine self-administration during daily sessions consisting either of 100 trials at an inter-trial interval of 90 sec or 10 trials at an inter-trial interval of 900 sec. For the 90 sec: 100 trial condition, unit injection doses of 1, 3, 10, 30, 100 and 300 mcg/kg/inj. have been assessed by dose-substitution for 5 consecutive sessions; for the 900 sec: 10 trial condition, unit injection doses of 10, 30, 100, 300, 1000, and 3000 mcg/kg/inj. have also been assessed by dose-substitution for 5 consecutive sessions. Despite appreciable variation of the inter-trial interval (90 vs 900 sec) and the total amount of drug intake available per session, results show that unit injection dose remains the primary determinant of response-probability across these varied conditions.

(v) Morphine self-administration during daily sessions consisting of 40 discrete-trials at an inter-trial interval of 50 sec, adulterating each unit injection of morphine (100 mcg/kg/inj.) with graded doses of naloxone (0.1 - 100 mcg/kg/inj.) for 5 consecutive sessions in each case. Results show that naloxone failed to suppress morphine self-injection behaviour consistently; consequently, the series of naloxone doses used to adulterate each unit injection dose of morphine is being replicated under conditions in which self-administration is maintained by a smaller unit injection dose of morphine (30 mcg/kg/inj.).

(vi) Morphine self-administration during daily sessions consisting of 40 discrete-trials at an inter-trial interval of 50 sec. Preceding every second or third session, monkeys received a single i.m. injection of naloxone at doses of 0.1 - 10 mg/kg. When compared with the effects of saline substitution or i.m. (presession) injection of saline, morphine (100 mcg/kg/inj.) self-administration was not appreciably suppressed by naloxone pretreatment. The experiment is being repeated, under conditions in which active self-administration of morphine is maintained by a smaller unit injection dose (30 mcg/kg/inj.). It has, however, been found that the suppression of morphine self-injection behaviour produced by a (presession) i.m. injection of morphine (3, 5.6, 10 mg/kg) can be reversed by a second, (presession) i.m. injection of naloxone (1-3 mg/kg). In separate (control) experiments, naloxone over an identical range of doses exerts no detectable effect upon cocaine-reinforced responding (30 or 100 mcg/kg/inj.) in monkeys.

(vii) Although the preceding experiments afford useful information concerning morphine dependence, they also afford stable drug intake baselines to assess the effects of intracerebral micro-injections of drugs with antagonist or mixed agonist-antagonist properties upon the monkey's propensity to repeatedly self-inject morphine. Bilateral microinjection cannulae have been implanted stereotaxically into a number of subcortical sites which, on the basis of other recent work[8], are known to be implicated in the antinociceptive central action of morphine. Experiments are in progress to determine the effects of bilateral microinjections of naloxone (10-30 mcg) upon i.v. morphine self-injection behaviour at specific subcortical sites in the brain (e.g., dorso-medial thalamus).

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[8] e.g., Pert, A. and Yaksh, T., 1974. Brain Res., 80, 135-140.

2. EFFECTS OF NARCOTIC ANALGESIC DRUGS UPON SCHEDULE-CONTROLLED BEHAVIOUR IN MONKEYS

Experiments have been completed, or are in progress, to assess the effects of morphine, naloxone and nalorphine, given alone or in combination, upon patterns of responding engendered by fixed-interval (FI) schedules of electric-shock presentation[9], comparable FI schedules of food-presentation and free-operant schedules of electric-shock postponement. Present data clearly indicate that morphine (0.1 - 10 mg/kg i.m.) increases shock-maintained responding at doses of 0.1 and 0.3 mg/kg but suppresses responding at higher doses. Suppression of responding by morphine is readily reversed by naloxone (0.1 - 3.0 mg/kg i.m.) in a dose-dependent manner. Response rate increases following low doses of morphine (e.g., 0.3 mg/kg i.m.) have not been observed when responding is maintained by the scheduled presentation of food-pellets, though the suppressive effects of morphine were readily reversed by i.m. injection of naloxone (0.1 - 3.0 mg/kg i.m.). Naloxone alone has been found to produce increases in responding maintained by the scheduled presentation of electric-shocks or food-pellets. Experiments have been completed dealing with the effects of morphine and naloxone upon fixed-ratio (FR50 and FR 200) schedules of electric-shock avoidance[10]. Work is also in progress to assess the effects of naloxone upon responding under schedules of shock-avoidance in non-tolerant and morphine-tolerant monkeys. Investigating changes in behaviour directly induced by narcotic analgesic drugs and their antagonists provides specific information about some properties of these drugs that may form an essential element in the interpretation of results obtained from morphine self-injection experiments.

3. SCHEDULE-INDUCED POLYDIPSIA AND ORAL INGESTION OF DRUGS

Two experiments, using rats, have been completed to assess the effects of morphine (2.5 - 30 mg/kg i.p.) and naloxone (0.3 - 30 mg/kg i.p.) injected separately, or in combination, upon schedule-induced water and schedule-induced morphine (0.75 mg/cc) polydipsia. Results showed that i.p. injection of morphine suppressed lever-pressing and oral intake of either water or morphine in solution. Naloxone reversed the suppressive effects of morphine. It was also found that the dose of morphine required to suppress oral intake of the drug was larger than the dose required to suppress water intake under comparable experimental conditions; this shift to the right of the morphine dose-effect curve after protracted oral ingestion of morphine, when compared with the effects of morphine upon water ingestion, can be interpreted as a manifestation of tolerance. Oral morphine or water ingestion diminished when food-pellets were no longer delivered as a consequence of lever-pressing. These results show that animals which are not physiologically-dependent upon morphine can be induced to ingest substantial amounts of the drug (approximately 50 mg/kg/hr) within relatively brief periods of time each day.

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9 e.g. Stretch, R. et al., 1968. Science, 162, 583-586; Stretch, R. et al., 1970. Can. J. Psychol., 24, 117-126. Orloff, E.R. and Stretch, R., 1975. Psychopharmacologia, 45, 29-37.

10 e.g. Stretch, R., and Skinner, N., 1969. Psychopharmacologia, 16, 89-104.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Gordon W. Wood	Chemistry

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Windsor, Windsor Ontario N9B 3P4

PROJECT TITLE TITRE DU PROJET Application of Field Desorption Mass Spectrometry to Rapid Identification of Drugs of Abuse

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-76	$5800.00	519 253-4232

FIELD OF RESEARCH SUJET DE LA RECHERCHE

[ ] EVALUATION ÉVALUATION	[X] BIOMEDICAL BIOMEDICALE	[ ] BEHAVIORAL COMPORTEMENT	[ ] SOCIAL SCIENCE SCIENCES SOCIALES	[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Through use of a variety of pure drugs as model compounds, field desorption mass spectrometry has been shown to be a selective technique for the identification of individual compounds and simple mixtures. Direct addition of the sample in solution to the field anode gives sensitivities in the low ng range.

Several approaches to isolation of drugs and metabolites from urine have been tried. The requirement that field desorption samples be free of sodium ions has severely hampered this work. Since this problem is not limited to drug samples, present work on elimination of alkali metal salt interference is being focussed on samples from other sources. Demonstration of the utility of this technique for practical problem solving has yet to be achieved.

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NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Noe ZAMEL, M.D. Noe Zamel	Medicine

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Toronto, Toronto, Ontario.

PROJECT TITLE – TITRE DU PROJET Reversibility of Pulmonary Function Abnormalities in Cigarette Smokers after Cessation of Smoking.

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975 - 1976	$26,000.00	416-596-4473

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[X] BIOMEDICAL – BIOMÉDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[ ] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Brief Description of Research Project:

The project is designed to evaluate the reversibility of pulmonary function abnormalities after cessation of cigarette smoking in individuals with different alpha-1-antitrypsin phenotypes. Extensive studies will include maximum expiratory flow volume curves on air and helium, static pressure-volume curve, closing volumes, slope of Phase III, frequency dependence of dynamic compliance, moment analysis of the spirogram, lung volumes and lung diffusion. These tests are performed both at the beginning and at the end of an eight-week period of abstention from cigarette smoking, and results are compared.

Summary of Key Findings:

Of the initial group of 16 MM alpha-1-antitrypsin phenotype individuals tested 11 (68%) were successful in abstaining from cigarette smoking. Analysis of the successful candidates' data revealed statistically significant changes in the pressure-volume curves, frequency dependence of dynamic compliance and volume at which maximum expiratory flow becomes density independent.

Relevance of the Project:

The relevance of this project covers several areas, such as establishing which aspects of pulmonary functions may be reversible and the problem of variation in susceptibility to cigarette smoke among people with MM versus MZ alpha-1-antitrypsin phenotypes.

Future Directions:

We have already done initial testing on a further 15 volunteers who will be returning after 8 weeks of abstention. Our sources of volunteers have been hospital staff and participants in cessation of smoking clinics; these have provided us with a continuous stream of subjects and we feel optimistic that such will continue to be the case.

We are also endeavouring to contact a number of known MZ alpha-1-antitrypsin phenotype subjects in order to pursue this aspect of our study.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR
Drs. K.W. Hindmarsh and N.W. Hamon

DEPARTMENT – DÉPARTEMENT
Pharmacy

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Saskatchewan, Saskatoon, Saskatchewan S7N OWO

PROJECT TITLE – TITRE DU PROJET
Development of Rapid Forensic Procedures for the Analysis of Selected Drugs

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-75 1975-76	1974-75--$10,540 1975-76--$17,970	343-4780 343-4789

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

[X] Analytical EVALUATION ÉVALUATION	[ ] BIOMEDICAL BIOMEDICALE	[ ] BEHAVIORAL COMPORTEMENT	[ ] SOCIAL SCIENCE SCIENCES SOCIALES	[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

ABSTRACT

Methods for the simultaneous identification and quantitation of diphenhydramine and methaqualone in urine and blood, have been investigated. Suitable thin-layer (TLC), gas (GLC) and liquid (LC) chromatography procedures have been developed. Nineteen TLC systems were investigated and of these eighteen were rejected either because of their inability to achieve separation of the standard drugs in a mixture, or because of their inability to separate one or both of the compounds from interferring substances in the urine. Silica gel GF plate developed first in $CHCl_3$/MeOH (90/10) to a height of 10 cm, dried and developed secondly in $CHCl_3$ (20 cm) gave R_f values of 0.76 and 0.30 for methaqualone and diphenhydramine respectively. Sequential spraying with 5% sulfuric acid, iodoplatinate and Dragendorffs reagent resulted in lower limits of detection of 0.6 µg for methaqualone and 0.15 µg for diphenhydramine.

An investigation of glc systems indicated a 3% OV-17 column was capable of separating methaqualone and diphenhydramine, generating reproducible, sharp peaks, free from interfering compounds (retention times 2.5 min and 7.3 for diphenhydramine and methaqualone respectively).

The following liquid chromatography columns were investigated; Sil-X-II; Octadecyl-Sil-X-II reverse phase, Cyano-Sil-X-I and Ion-XSC. Various solvents, pH, temperature changes and flow rates were investigated. The Ion-XSC column was, using a borate buffer, found satisfactory for separation of the two drugs.

A number of extraction procedures were investigated. Standardized extraction methods (i.e. shaking for certain periods of time with certain solvents, etc.) had to be used in order to get consistant quantitative recoveries. Of all the methods examined, the use of a charcoal cartridge appeared to be superior and has a number of advantages: Using a cartridge there is standardization in the amounts of charcoal used. The method is sensitive, microgram quantities being easily isolated. No filtration or centrifugation steps are required. Handling of biological samples is practically eliminated. Large volumes of urine can be extracted fairly rapidly. Isolation costs are minimal, preparation of the cartridges involves little time. Pretreatment of the cartridge is not necessary before extraction. The pH of the biological fluid does not have to be adjusted for extraction. With the exception of enzyme hydrolysis, the charcoal cartridge was superior in isolating the drugs from human urine after the ingestion of Mandrax. Unfortunately, enzyme hydrolysis is time consuming and it is important in Forensic Analysis to have rapid extraction procedures.

The use of the charcoal cartridge is being further explored for the isolation and quantitative recovery of other drugs subject to abuse. Investigations will include isolation of acidic, neutral and basic drugs from biological fluids and perhaps tissues.

Publications

1. K.W. Hindmarsh, N.W. Hamon, D.F. LeGatt, "Use of a Charcoal Cartridge in Isolating Basic Drugs from Urine, Clin.Chem. 21, 1852 (1975).

2. K.W. Hindmarsh, N.W. Hamon, D.F. LeGatt, "The Simultaneous Identification and Quantitation of Diphenhydramine and Methaqualone in Biological Fluids," Submitted for publication, Clin. Toxicol.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
M.G. Joneja	Anatomy

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE

Queen's University, Kingston, Ont.

PROJECT TITLE – TITRE DU PROJET

Teratogenic and cytogenetic effects of marihuana and Δ^9-THC in rodents

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1973-4, 1974-5, 1975-6	19,910, 18,960, 14,220	(613) 547-2600

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [X] EVALUATION ÉVALUATION; [ ] BIOMEDICAL BIOMEDICALE; [ ] BEHAVIORAL COMPORTEMENT; [ ] SOCIAL SCIENCE SCIENCES SOCIALES; [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This project deals with the evaluation of teratogenic and cytogenetic effects of Δ^9-tetrahydrocannabinol (Δ^9-THC) in experimental laboratory rodents. Previous studies with cannabis extracts of unknown composition have been shown to produce significant congenital anomalies in rodents but pure Δ^9-THC which is the principal psychoactive compound has been found to be non-teratogenic

Teratological Experiments:

Swiss Webster mice: Δ^9-THC was administered to pregnant mice by three routes, iv, sc, and po. The doses used varied in each series and were generally less than 2/3 of the adult LD50. Single injections were given on a specific gestational day from 7 to 11. In a separate experiment, serial injections were also given during the critical period of organogenesis. Untreated and vehicle treated controls were used in all series. All examinations were done on day 18. Fetal mortality, fetal weights, external and internal malformations and skeletal defects were examined. Single and multiple iv doses of 10 and 20 mg/kg Δ^9-THC did not produce any significant effects on the fetuses except growth retardation in some samples. Subcutaneous dose levels ranging between 3.0 and 300 mg/kg were given on one of days 7 to 11. In this series also a significant reduction in fetal weights was observed. Although a low frequency of up to 3.9% abnormal fetuses was found in some Δ^9-THC treated samples, and was higher than the untreated control values of <1%, this incidence was not statistically significant at 95% confidence level. Razor blade sections did not reveal any internal anomalies, nor were any significant skeletal defects found. Intragastric series received single doses of 100, 200 and 400 mg/kg on days 7 to 11. Fetal weights were significantly reduced in many samples and 12.1% of the live fetuses from dams given 400 mg/kg Δ^9-THC on day 9 were abnormal. This value was significantly higher ($p<0.05$) than the corresponding controls. Higher dose (400 mg/kg - day 10) also produced skeletal defects such as fused ribs and asynchronous vertebral ossification. Multiple injections were given at dose levels of 25, 50 and 100 mg/kg on days 7 to 10, 9 to 12, and 7 to 12. In this series, no significant gross or skeletal anomalies were produced.

DBA mice: In this experiment po doses of 100, 200 and 400 mg/kg Δ^9-THC were given on each of days 7 and 11. The overall sensitivity of this strain of mice was greater than that of Swiss Webster. As compared to controls, the frequency of abnormal fetuses was significantly higher ($p<0.05$) in dams given 400 mg/kg Δ^9-THC on gestational day 8 or 9 and in dams given 200 mg/kg Δ^9-THC on day 10. The latter group had 22.7% abnormal fetuses. In addition, skeletal defects and visceral defects were also found in some samples.

These data have shown that only large po doses of Δ^9-THC were significantly teratogenic; iv injections were ineffective and sc exposure produced a very low frequency of abnormal fetuses. Moreover, a clear dose-response pattern was not observed in these experiments. Therefore, the possibility of an indirect action of Δ^9-THC by interfering with gastro-intestinal functions of the mother cannot be excluded in the case of teratogenic response to large po doses. It appears that the high teratogenic activity of cannabis extracts reported previously may have been due to interaction of Δ^9-THC with other cannabinoids or with impurities.

Golden Syrian hamster: Single po doses of 125, 250 and 500 mg/kg Δ^9-THC on days 7 to 12 and multiple doses of 25, 50 and 100 mg/kg Δ^9-THC on days 7-10, 9-12 and 7-12 have been tested in hamster to determine if any species differences exist. Preliminary data indicate that the

teratogenic response of hamster to Δ^9-THC is similar to that of mice; only large doses producing gross external or skeletal defects.

Cytogenetic analysis: Bone marrow cells from young adult hamsters (100g) were examined for the effects of Δ^9-THC on proliferating cells at 6,12,24,48 and 96 hours after sc injections of Δ^9-THC. Even extremely high dose of 1 gm/kg did not show any clastogenic effects on chromosomes. Chromosome breakage rate was about 1.7% in controls and Δ^9-THC groups showed only up to 2.0% in some samples. Karyotype anomalies were also not induced by Δ^9-THC. However, mitotic index was significantly reduced in Δ^9-THC samples at 6,12 and 24 hours with 1 gm/kg and 10mg/kg. Further studies are in progress.

Summary of key findings: Single large po doses (200mg/kg and 400mg/kg) of Δ^9-THC were found to be teratogenic in Swiss Webster and DBA mice. The lack of teratogenicity by lower iv, sc and po doses suggests the possibility that pure Δ^9-THC is highly unlikely to be teratogenic in humans, barring some unusual species differences. Whether interaction of Δ^9-THC with other cannabinoids or impurities would produce synergistic effects is not known. Preliminary data on cytogenetic effects of Δ^9-THC on proliferating hamster bone marrow cells indicate no significant chromosomal damage or karyotypic alterations. A suppression in mitotic activity is, however, evident within 24 hours after injection of 10mg/kg Δ^9-THC.

Significance of project: Since cannabis is consumed by young individuals during their reproductive life, the possibility exists that the pattern of development, growth and behaviour may be influenced by the adverse effects of the drug on the developing fetus and on the genetic material. Since Δ^9-tetrahydrocannabinol is the principal psychoactive component of cannabis, it is essential that effects of this compound must be fully understood and compared with those produced by crude extracts.

Future directions: The lack of teratogenicity by low doses of Δ^9-THC and significant teratogenic response to crude extracts, suggest the logical direction should be to determine whether the cannabis extracts with known Δ^9-THC potency are teratogenic and whether or not presence of other cannabinoids enhances the teratogenic activity of Δ^9-THC.

Publications:

Joneja, M.G. A study of teratological effects of intravenous, subcutaneous and intragastric administration of Δ^9-tetrahydrocannabinol in mice. Toxicol. Appl. Pharmacol. (1976) Accepted. (In press).

Joneja, M.G. Effects of prenatal exposure to Δ^9-tetrahydrocannabinol in DBA mice and syrian hamster. Proc. 4th Pan Amer. Congr. Anat. p. 20. 1975.

Joneja, M.G. Effects of Δ^9-tetrahydrocannabinol (THC) on fetuses of Swiss Webster mice. Anat. Rec. 181: 387-88. 1975.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
E.E. Knaus and R.T. Coutts	Faculty of Pharmacy
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Alberta; Edmonton, Alberta	
PROJECT TITLE – TITRE DU PROJET New Analytical Techniques for the Separation, Identification and Quantitation of Cannabinoids and their Metabolites.	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
1974 - 76	$13,874

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE AC 403-432-5993

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [✓] EVALUATION ÉVALUATION; [ ] BIOMEDICAL BIOMÉDICALE; [ ] BEHAVIORAL COMPORTEMENT; [ ] SOCIAL SCIENCE SCIENCES SOCIALES; [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Methods for the separation, identification and quantitation of cannabinoids present in hashish have been developed. These methods include high pressure liquid chromatographic and gas liquid chromatographic separation of cannabinol (CBN), Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC) and cannabidiol (CBD) as well as their t-butyldimethylsilyl ether and trimethylsilylacetate derivatives. The necessity for internal standards, the sensitivity of the method (HPLC) and the mass spectral fragmentation pathways for the t-butyldimethylsilyl derivatives have been studied.

HPLC parameters have been developed which allow, for the first time, separation of Δ^8-THC and Δ^9-THC. Biphenyl was found to be a suitable internal standard for HPLC quantitation of the natural cannabinoids.

The trimethylsilylacetate (TMSA) and t-butyldimethylsilyl (TBDMS) derivatives were found to be both thermally and hydrolytically stable during HPLC and GLC analyses. These derivatives are also applicable to the analyses of tetrahydrocannabinol metabolites. Codeine was found to be a suitable internal standard for GLC analyses of these derivatives.

The methods and techniques developed in the study should find widespread application for routine analysis of cannabinoids and their metabolites. The derivatization techniques should also be applicable to other areas of Drugs of Abuse. The HPLC separations of cannabinoids are valuable since it is expected that HPLC-MS will soon become as useful as GC-MS.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
George Laverty, Marilyn Bowman, Paul Rosenbaum	Kingston Psychiatric Hospital, Depts. of Psychology and Sociology.
INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE	
Queen's University, Kingston, Ontario	

PROJECT TITLE — TITRE DU PROJET

Treatment Programme Development Research in Frontenac County

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
4 years, 4 months	$298,027	(613)-547-2622

FIELD OF RESEARCH — SUJET DE LA RECHERCHE

- [x] EVALUATION — ÉVALUATION
- [ ] BIOMEDICAL — BIOMEDICALE
- [ ] BEHAVIORAL — COMPORTEMENT
- [ ] SOCIAL SCIENCE — SCIENCES SOCIALES
- [ ] MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

The Treatment Development Team in Kingston is one of six research groups across Canada conducting an in-depth study of the relationship between alcohol and other drug problem clients and the treatment community. The treatment development approach involves the establishment of a constructive working relationship with the treatment community in order that both researchers and treatment persons may guide the research process and implementation of findings. Thus, the formative model is being used, rather than the summative, or short-term method, of treatment evaluation.

During Phase 1, the focus of the research was on studying a small number of agencies in-depth and on developing measurement instruments. In addition, continuing contact has been maintained with community treatment agencies in terms of analyzing the Referral Network and working with the community to improve this network. Phase I has been completed, which yielded three major instruments, the Staff In-depth Interview (focusses on staff attitudes), the Client Information Form (acts both as an intake form and an evaluating tool) and the Natural History Analysis (an instrument to collect, in detail, a client's history to look for typical problem and treatment patterns). The staff attitude data have been analyzed, resulting in a number of clusters, which should contribute to the development of agency types.

Thus, the project has both a pure research component (attempting to match specific types of clients with types of treatment) and an applied component (working on an individual basis with agencies and with a representative number of agencies to improve the referral network).

During Phase II, the emphasis will primarily be on collecting information on clients, using both the Client Information Form and the Natural History Analysis. In addition, the Referral Network will be experimentally studied, based on the Core-Shell Model.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Stephen L. Milstein, Ph.D.	I.R.N.S. Santé
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	Université du Québec, Institut national de la recherche scientifique
PROJECT TITLE – TITRE DU PROJET	Traitment de l'abus des Drogues: Recherche et Developpement

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-78	$376,636.00	253-2852

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: [x] EVALUATION – ÉVALUATION; [ ] BIOMEDICAL – BIOMEDICALE; [ ] BEHAVIORAL – COMPORTEMENT; [ ] SOCIAL SCIENCE – SCIENCES SOCIALES; [ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

Ce projet a été élaboré à la suite d'une initiative de la Direction de l'Usage Non-Médical des Drogues visant à établir des interactions entre des équipes multidisciplinaires de recherche et des équipes de soignants, dans le but de développer des méthodes de recherche et d'évaluation des moyens thérapeutiques utilisés dans le traitement de l'abus des drogues.

Le projet proposé a pour but ultime d'aider les soignants, engagés dans le traitement et la réadaptation de l'abus des drogues, dans la mise au point de programmes de traitement plus efficaces et dans l'utilisation plus rationnelle des compétences et des ressources.

Durant la première année, un ensemble de données sur l'état actuel des traitements dans le domaine de l'abus des drogues ont été receuillies et des méthodes permettant l'évaluation des processus et des techniques thérapeutiques ainsi que l'évaluation de l'état clinique ont été mises au point.

Durant cette deuxième année, nous avons déterminé les buts des programmes de traitement et avons fourni des outils d'évaluation visant à mesurer l'efficacité des traitements en cours et la normalisation de ces outils (questionnaires) pour trouver les caractéristiques propres à la population traitée en fonction du centre de traitement.

CE PROJET COMPREND TROIS PHASES

PHASE A: Identification et description des programmes de traitement de l'abus des drogues:

1. Identification des programmes au niveau fédéral, provincial et privé en cours dans la région de Montréal.
2. Description des objectifs poursuivis par ces programmes tant du point de vue des malades que des soignants et des organismes de subvention.
3. Description complète des processus thérapeutiques.

PHASE B: Mise au point et validation des instruments et des techniques de mesure.

PHASE C: Mise au point d'un centre d'information et de consultation pour les équipes.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT DEPARTEMENT
JOHN P. J. PINEL	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of British Columbia, Vancouver, B.C. V6T IW5, Canada

PROJECT TITLE – TITRE DU PROJET
Development of Alcoholism Treatment Programs in British Columbia: Biomedical Treatment Modalities

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER NUMÉRO DE TÉLÉPHONE
1974-1976	$21,657.81	(604) 228-4656

FIELD OF RESEARCH SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION [X] BIOMEDICAL BIOMEDICALE [X] BEHAVIORAL COMPORTEMENT [X] SOCIAL SCIENCE SCIENCES SOCIALES [X] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The major objective of the NMUD Treatment Development Program is the support of research efforts directed toward the development of more effective drug abuse treatment and prevention programs. The initial year of support (Phase One) under this program was specified as a non-experimental period to enable research teams to develop community contacts, to gain access to treatment programs, and to gather preliminary data on the drug abuse treatment networks in their respective localities.

During this preparatory year of support, we identified three problems which had to be resolved before program evaluation could be conducted by our team. The first problem was the unsettled political climate in B.C. at the time. The reorganization of drug abuse treatment agencies had produced a climate of uncertainty in which lines of authority were ambiguous and the fate of many programs was in doubt. This state of flux was hardly conducive to evaluation research or program development. The second problem we identified was the dearth of innovative, biomedical treatment programs in B.C. There were no established inpatient facilities for chronic alcoholics in the province; nor were there any innovative, biomedical programs for chronic alcoholism. Most alcoholism programs offered a counselling format with an A.A. orientation. Since there have been numerous evaluations of these programs, another such study would have been of negligible value to the NMUD treatment development program. The third problem we had to deal with was the lack of other treatment development teams in Vancouver. Due to the lack of a long-established tradition of collaboration between research teams and drug treatment agencies, we were obliged to stimulate the development of a multidisciplinary team of professional drug abuse researchers.

These three initial problems were resolved successfully during the course of Phase One. First, we have established a strong liason with the major alcoholism treatment agency in Vancouver. Second, we are prepared to conduct an experimental study of a biomedical treatment modality-disulfiram implantation - in the treatment of chronic alcoholics at this agency. Third, the recent involvement of several professional drug-abuse researchers in NMUD-related activities guarantees a fund of expertise and the opportunity for graduate students to involve themselves in drug abuse program development in community settings.

The approach which we have adopted to assist in the development of innovative drug treatment programs closely approximates the "service model" strategy developed by Libo (1974). This approach entails offering our services and skills to community treatment agencies, thereby establishing that we can provide them with a reliable service which can help them to solve their own problems. We are now actively working to assist one drug-abuse agency in developing innovative, biomedical treatment programs. Our immediate goal is to conduct a double-blind, placebo-control evaluation of the clinical efficacy and modes of action of disulfiram implants. Having established a strong liason with community agencies, our long-term goal is to assist interested drug-abuse agencies in developing a variety of biomedical treatments with built-in treatment evaluation components.

Libo, L. "A Research-versus-Service Model for Training in Community Psychology". American Journal of Community Psychology, 1974, 2, 173-177.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Dr. Angus E. Reid	Social and Preventive Medicine

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE

University of Manitoba, 753 McDermot Avenue, Winnipeg, Manitoba R3E 0W3

PROJECT TITLE - TITRE DU PROJET

KNOWLEDGE AND SOCIAL ACTION: A STUDY OF THE IMPACT OF RESEARCH ON ALCOHOL AND DRUG TREATMENT PROGRAMS IN CANADA

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
Jan 1, 1976 - March 31, 1978	$120,360.00	(204) 786-4321

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [XX] EVALUATION ÉVALUATION; [ ] BIOMEDICAL BIOMÉDICALE; [ ] BEHAVIORAL COMPORTEMENT; [ ] SOCIAL SCIENCE SCIENCES SOCIALES; [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The rationalization of human activity through the use of scientific knowledge is one the hallmarks of what has been termed the 'post industrial society'. In the public policy area, scientific knowledge (acquired through research and evaluation) promises the development of more effective and efficient social programs. This promise has however yet to be fully realized. Experience during the 1960's in Canada and other Western nations suggests that many, if not the majority, of program research endeavours fail to realize their full potential as agents for organizational development and change.

The present study proposes to examine the role of research in drug treatment program development in Canada. Specifically, the following questions are addressed: What impact does research and evaluation have on the development of alcohol and drug treatment programs? Are certain types of programs more than others the result of research? To what extent is the attempt to rationalize treatment programs through research and evaluation facilitated or impeded by constraints on a provincial or federal level?

In order to examine these questions two complementary research strategies are proposed. (1) A national study of alcohol and drug treatment programs aimed at gathering retrospective information on the nature of program oriented research with which agencies have been associated; the changes which have taken place in these treatment programs; and the structural and ideological characteristics of the agencies and their environments as related to change. (2) A prospective, qualitative study of four Winnipeg agencies currently involved in developmental research.

Both components of the study are informed by a theoretical model developed on the basis of field studies during the past year. The model attempts to explain changes in treatment technology and staff and client characteristics with reference to three classes of variables. (1) The nature of research as distinguished by the methods employed, the relationship of researchers of the agency being studied, and the purpose of the research. (2) The structure and ideology of treatment agencies with emphasis on the role of complexity, centralization, formalization, professionalization

and agency goals in mediating the impact of research .

(3) The structure and ideology of the external environment.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
R.A. Ruotolo	

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Association for Human Relations & Counselling Ltd.

PROJECT TITLE — TITRE DU PROJET The Atlantic Region Research and Development Team for Drug Treatment Problems

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975 1976	$40,000.00	425-5000

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
[X] EVALUATION ÉVALUATION
[ ] BIOMEDICAL BIOMEDICALE
[ ] BEHAVIORAL COMPORTEMENT
[ ] SOCIAL SCIENCE SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Purpose

The overall purpose of our research in phase one (1) was to establish comprehensive descriptions of drug treatment programming in each of the four (4) provinces of the Atlantic region with a view to developing adequate framework(s) for future research.

This major objective was approached through two (2) related, complementary research designs:

i) organizing the documentation of existing drug treatment programs in the four (4) provinces in order to develop models of treatment networks; and

ii) an in-depth analysis of the service delivery system of the Cape Breton Regional Pilot Project of the Nova Scotia Commission on Drug Dependency to define existent intra-relationships within components of regional programming and their inter-relationships with other human services in the region.

For the most part, data gathering for both designs involved an in-depth interview procedure augmented by a secondary analysis of existing documentation. In the second design (analysis of Cape Breton Region Pilot Project) this was supplemented by information obtained through participant observation.

Thus far, analysis of data has proceeded only within the context of the second design (analysis of Cape Breton Region Pilot Project). In terms of the identified "felt needs" of Cape Breton regional staff, data has been analysed and summarized through the formation of the following categories: (1) Treatment Program Development, Staff Development and Organizational Development.

With a view to facilitating treatment program development, preparation and arrangements for interim information feedback sessions to Cape Breton regional staff are now in the process of completion.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER AND OF SIGNATURE DU CHERCHEUR — DEPARTMENT - DÉPARTEMENT

Dr. J. A. Wada — Psychiatry - Neurosciences Division

INSTITUTION AND ADDRESS - ÉTABLISSEMENT ET ADRESSE

Health Sciences Center Hospital, University of B.C. Vancouver, B.C.

PROJECT TITLE - TITRE DU PROJET

Preclinical Evaluation of the Antiepileptic Properties of CANNABIS SATIVA

YEARS FUNDED - ANNÉES SUBVENTIONNÉES | FUNDS ALLOCATED - SUBVENTIONS ASSIGNÉES | TELEPHONE NUMBER - NUMÉRO DE TÉLÉPHONE: 228-2556

FIELD OF RESEARCH - SUJET DE LA RECHERCHE: [X] EVALUATION - ÉVALUATION; [ ] BIOMEDICAL - BIOMÉDICALE; [ ] BEHAVIORAL - COMPORTEMENT; [ ] SOCIAL SCIENCE - SCIENCES SOCIALES; [ ] MULTIDISCIPLINARY - MULTIDISCIPLINAIRE

I: BRIEF DESCRIPTION OF RESEARCH PROJECT

1) Antiepileptic effects of cannabis

a) Rats - we examined the acute antiepileptic effect of intraperitoneal injections of Δ^9THC on clinical and electrographic seizure activity evoked by electrical stimulation of the amygdala in freely moving rats. The rats were subjected to a kindling procedure after a further period of seizure development wherein the stability of the evoked seizures was established, and then the drug trials were initiated. Dose-response relations were determined by using multiple injections in each rat, but 7 or more days intervened between each injection to prevent tolerance or cumulative effects. Either 1 mm/kg or 5 mm/kg of Δ^9THC was sufficient to reduce or block the clinical and usually, the electrographic manifestations of kindled amygdaloid seizures in all the rats tested. These effects were measureable only on the day of drug administration and not in subsequent sessions. Toxic behavioral reactions were evident at 5 mm/kg but not at 1 mm/kg dose. Preliminary results with injections of Δ^8THC were also obtained. We conclude that Δ^9THC can exert acute antiepileptic effects against kindled amygdaloid seizures in rats, and that these effects can occur at doses that need not necessarily produce gross behavioral toxicity.

b) Cats - treatment of freely moving cats with Δ^9THC temporarily reduced the clinical and electrographic seizure activity induced by electrical stimulation of subcortical structures. The antiepileptic effects are not accompanied by gross signs of behavioral toxicity. Seizure activity induced by hypothalamic stimulation seemed to be more sensitive to this drug than that induced by stimulation of dorsomedial nucleus of the thalamus.

c) Baboons - the data obtained to date suggests that Δ^8THC and Δ^9THC exert their antiepileptic effects through suppression of afterdischarge propagation through the established route of convulsive activity in the amygdaloid kindled convulsion in Senegalese baboons. This finding contrasts with the total ineffectiveness of the same agent upon flicker-induced photomyoclonic seizure in this species.

2) Prophylactic property of cannabis

a) Cats - our observations suggest that Δ^9THC is more potent that Δ^8THC in its antiepileptic property and Δ^8THC has potent suppressive effect on the kindling process, but not upon the established kindled state. This property of cannabis is comparable to that of well-established anticonvulsants such as phenobarbital and carbamazepine according to our previous study and it appears far superior to that of diphenylhydantoin. Whether the demonstrated prophylactic potency of Δ^9THC also applies to seizure development by stimulation of different brain sites such as frontal cortex, remains to be determined.

CANNABIS ABSTRACT Continued . . . .

b) Rats - acute but not chronic administration of a higher dose of Δ^8THC and Δ^9THC induced a linear-dose response effect. In prophylactic study, clinical seizure development, but not afterdischarge duration, was significantly retarded by Δ^9THC. However, when subjected to re-kindling, these animals required a significantly fewer number of amygdaloid stimulation and controls. This finding suggests that the prophylactic potency of Δ^9THC under this experimental condition is not as marked as that previously found in cats. Such difference may be due to either species difference or difference in techniques used to kindle the two species. We suspect the latter is the likely cause and this possibility is being examined at present.

II: KEY FINDINGS

Components of Cannabis have a significant anticonvulsive and prophylactic potency with respect to amygdaloid seizure developemnt in certain species of animals

III: SIGNIFICANCE OF THE PROJECT

The findings obtained so far suggest that this compound may have a potential of being medically useful provided its psychoactive property can be reduced or eliminated.

IV: FUTURE DIRECTION OF RESEARCH PROJECT

Possibility of pharmacological prophylactic potency of various components of cannabis in terms of epileptic seizure development is being examined in subhuman primates.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Paul F. Zelhart, Ph.D.	Psychology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE

Department of Psychology, University of Alberta, Edmonton, Alberta T6G 2E1

PROJECT TITLE — TITRE DU PROJET Non-Medical Use of Drugs Treatment Program Development Research: Alberta and District of MacKenzie, Northwest Territories.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
Sept. 1974 to June 1976	$135,000.00	432-5330

FIELD OF RESEARCH — SUJET DE LA RECHERCHE

[XX] EVALUATION — ÉVALUATION [ ] BIOMEDICAL — BIOMÉDICALE [ ] BEHAVIORAL — COMPORTEMENT [ ] SOCIAL SCIENCE — SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

Ad hoc evaluations of "success" (usually defined by criteria established outside the program) have been criticized as unrepresentative of the service process and its objectives. As a result they have done little to specify the nature of treatment programming and nothing to contribute to the improvement of services. Thus, it is necessary to improve the quality of evaluations--the validity of service descriptors, specifications of outcome and monitoring of impact. The method adopted is to develop a research technology focusing on the provision of information to be utilized in service development.

To have a positive impact on service development, evaluation must be built into rather than imposed upon the treatment program. The provision of information must be continuous rather than sporatic and must relate directly to the concerns of a program. To accomplish this, treatment personnel must become major contributors in the process of research and program evaluation. The term "enablement" has been used to describe the process by which treatment personnel acquire necessary skills in data collection, problem identification and interpretation of outcomes. Initially, this was accomplished on a one-to-one basis by involving the staff of each program in specification of research questions for their program, identification of their service interventions and the anticipated consequences of the service. While this has proven to be quite effective, and has exposed common areas of concern among programs, consideration must be given to the "costs" of maintaining the individualized format. Hence, development has proceeded toward more generalized workshop presentation and group methods in the initial phases of enablement.

A major thrust of the team has been the development of instruments which define the character of treatment programming within four interdependent sectors; the service target group, the service facility (including the physical plant and staff), the therapeutic modes of service (both "systematic" and "fortuitious" interventions) and the consequences of service ("anticipated" and "unanticipated"). These descriptors have been utilized in the preparation of a referral manual for "gate-keepers" (professionals outside the area of drug abuse programming) and in projects leading toward the development of client and service selection.

Research of general interest to treatment agencies has included the specification of the range and character of drug abuse in selected communities, the social and economic impact of drug abuse among natives, and the role of alcohol on crimes of violence and aggression. Research involving community attitudes toward drug abuse and its treatment, the follow-up of clients, identification of compliance to treatment, entering characteristics of clients, and the development of effective screening and referral systems has been conducted in association with particular agencies.

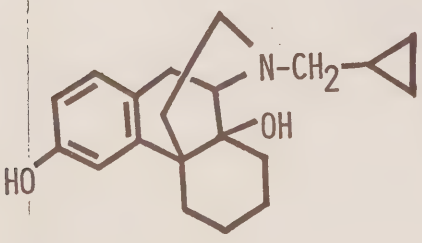
Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Bernard BELLEAU	Chemistry, Otto Maass Chemistry Bldg.
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
McGill University, P.O. Box 6070, Station A, Montreal, Quebec, H3C 3G1	
PROJECT TITLE – TITRE DU PROJET	
In vivo N-dealkylation of Opiates in Relation to Agonist-Antagonist Actions	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
(2) two years Dec. 1, 1974 Nov. 30, 1976	$32,841.00
TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE 392-5926	

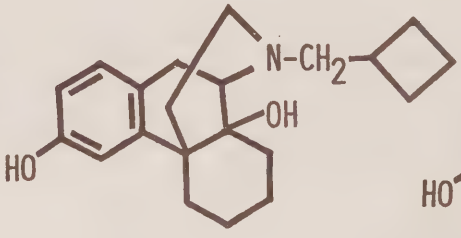
FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☒ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Brief description of research project: A key parameter affecting the overall pharmacological and physiological effects of narcotics is enzymatic N-dealkylation. The resulting nor-derivatives are potent narcotics when applied introcerebrally. Virtually all narcotic antagonists possess a N-substituent other than methyl but little is known about their effects on the morphine N-demethylase. Nalorphine has been claimed to inhibit the enzyme but the evidence is unclear since it is rapidly N-dealkylated in vivo. We have previously demonstrated (in man) that the presence of 14-hydroxyl (OH) group next to N-substituent of narcotic antagonists eliminates all the narcotic side effects while promoting analgesic activity. We speculated that this class of drugs may not suffer N-dealkylation. This could explain the lack of narcotic side effects since the narcotic nor-derivative would not be produced in vivo. Effective inhibition of enzymatic N-demethylation and N-dealkylation in both the liver and brain could serve to lessen the side effects of narcotics. We therefore decided to develop methodology in order to study the effect of various N-substituents and of 14-OH groups on liver N-demethylase (cytochrome P450). We also initiated studies on the possible N-demethylation of narcotics in brain tissue especially those regions rich in opiate receptors. New, sensitive, general and selective assay methods for the N-demethylases were investigated intensively.

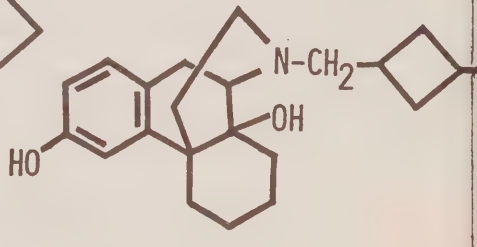
2. Summary of major developments. We have discovered that the chromotropic assay method previously used by several groups of investigators leads to false conclusions because it is not reproducible and measures only 20% of the total formaldehyde actually generated. It also cannot be used with other aldehydes. We therefore developed a new routine assay for any aldehyde using Purpald as the reagent. This development was very difficult technically and although applicable presently, we still have to find ways of eliminating one last source of interference. The new drugs Oxilorphan (I; a pure, orally effective antagonist) and Eutorphanol (II; a clean, potent non-narcotic analgesic in man) appear not to suffer N-dealkylation by the microsomal enzyme.



(I)



(II)



(III)

Instead, Butorphanol suffers hydroxylation on the cyclobutyl ring to give III which possesses a pentazocine-like pharmacological profile. On the other hand, brain regions known to be rich in opiate receptors (hypothalamus, medial thalamus and corpus striatum) possess narcotic N-demethylase activity, an observation recently made independently by another group in New York. It seems plausible then that N-dealkylation inhibition has an important bearing on the narcotic properties of opiates.

3. Importance of project: A practical solution to the problem of narcotics abuse consists in the development of non-narcotic, strong analgesics and antitussives so as to eliminate our dependence on opium as a source of drugs. The discovery of Butorphanol constitutes a first step in that direction and for the next generation of non-narcotic analgesics to be developed fully, the medicinal chemist will need basic information on those biotransformations that are relevant to structurally induced changes in the pharmacological profile of narcotics and their antagonists. Hence, the key importance of practical knowledge about the mode of interaction of these drugs with the N-dealkylases as this will guide the medicinal chemist in his choice of structures to be investigated. Structures that cannot suffer N-dealkylation (such as I and II; see metabolite III above) may not produce tolerance as is the case for I and II. Drug developers need this kind of information.

4. Summary of discoveries likely to reduce problems associated with the non-medical use of drugs. The development of a new, simple and routine assay for narcotic N-dealkylases and the observed unexpected resistance of the non-narcotic analgesic Butorphanol toward N-dealkylation (but susceptibility to side-chain hydroxylation) constitutes information that is presently useful to industrial medicinal chemists. Based on that knowledge, structural modifications of Butorphanol have already been designed and accomplished. Some of the resulting compounds are scheduled to undergo pre-clinical testing. The results may further lessen our dependence on opium which is a major source of illicit drugs.

5. We hope to further improve our new assay method for the liver and brain N-demethylase and screen about one dozen structural prototypes of narcotics and their antagonists to better delineate the requirements for resistance to or inhibition of the enzyme. The information will then be used by medicinal chemists to further develop the new generation of non-narcotic analgesics. We then hope, if funds are available, to study structure-activity relationships and metabolic degradation of Enkephalin (the "endogenous analgesic" pentapeptide recently discovered by Hughes and Aberdeen). It is our opinion that this new effector of the opiate receptor interacts with non-morphine sites and may thus lead the way to an entirely new class of analgesics devoid of any narcotic-like effects.

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
H.C.Fibiger/M.E.Corcoran	Neurological Sciences
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of British Columbia, Vancouver, B.C. V6T 1W5	
PROJECT TITLE – TITRE DU PROJET	
Neurochemical Substrates of Drug-Reinforced Behaviour	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
1974-1976	$ 63,700.

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE: 228-2984

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☒ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Humans self-administer a wide variety of drugs, but the factors underlying the initiation and maintenance of this behaviour remain obscure. It is likely, however, that at least part of the motivation for drug self-administration lies in the direct pharmacological reinforcing properties of the drugs in question. Support for this view comes from the observation that many drugs abused by humans are also self-administered by animals in situations where the only evident reinforcement for this behaviour is the drug itself. Previous pharmacological studies indicate that self-administration of drugs such as the opiates, ethanol, and psychomotor stimulants may depend on the availability of cerebral catecholamines; this is suggested by the finding that self-administration is reduced or eliminated by pretreatment with α-methyl-para-tyrosine, an inhibitor of tyrosine hydroxylase. These data led us to propose that ethanol, opiates, and psychomotor stimulants are self-administered because they facilitate the synaptic activity of central catecholaminergic pathways, which hypothesis leads to the straightforward prediction that selective and specific lesions of these pathways with 6-hydroxydopamine (6-OHDA) should block self-administration of the drugs. Our project is designed to test the prediction.

We have begun by examining the effects of 6-OHDA-induced lesions on the self-injection of cocaine by male rats. The dosage of cocaine available to the rats is 0.50 mg/kg/injection, and the lesions are made after the animals have established a stable baseline of self-injection behaviour. The preliminary results to date suggest that 6-OHDA-induced lesions of the noradrenergic pathways in the brain fail to have any reliable effect on the tendency of rats to self-inject cocaine. In subsequent experiments we shall examine the effects of lesions of the dopaminergic pathways

on self-injection of cocaine, and a similar analysis will be performed on the self-injection of drugs such as d-amphetamine, ethanol, and morphine.

It is hoped that these experiments will enable us to identify the location and nature of the neural pathways whose activity mediates the reinforcing effects of various drugs of abuse. In addition to their obvious theoretical interest, these experiments may result in the formulation of specific pharmacological strategies for dealing with drug abuse in humans.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Dr. W.F. Forbes (with Dr. W.H. Cherry)	Statistics
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
Faculty of Mathematics, University of Waterloo	
PROJECT TITLE – TITRE DU PROJET	
The Waterloo Smoking and Health Project	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
1974 to present	1976-1977 $200,000.
TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE	
(519) 885-1211 ext 3473	

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMÉDICALE ☐ BEHAVIORAL COMPORTEMENT ☐ SOCIAL SCIENCE SCIENCES SOCIALES ☒ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Description of the Project

A major aim of this project is to monitor the tar, nicotine and carbon monoxide deliveries of cigarettes available in Canada and, by the publication of the results, to encourage industry to make available less harmful cigarettes; that is, cigarettes delivering less tar, nicotine and carbon monoxide. The project consists of a number of interrelated programmes, designed to provide additional information pertinent to the development of such less hazardous cigarettes.

2. Summary of Key Findings

(a) Tar and nicotine deliveries of Canadian cigarettes have been determined on a regular basis, and a general downward trend in sales weighted tar deliveries has become apparent during the last six years.

(b) The carbon monoxide deliveries of cigarettes available in Canada have been estimated, and are related to tar and nicotine deliveries. Hence, a reduction in tar and nicotine deliveries can also be expected to lead to a reduction in carbon monoxide deliveries (see J.C. Robinson and W.F. Forbes, Arch.Envir.Health, 31, 425-434, 1975).

(c) Smoking habits of individual smokers have been investigated and it has been found that individual smokers can be classified into groups on the basis of questionnaires and measurements on cigarette butts.

(d) A survey of about 100,000 Canadian school children has been carried out, and it has been shown that an increase has incurred in the number of girl-smokers in all age groups.

(e) An econometric model for cigarette consumption, as it is affected by price and advertising expenditures, has been developed. The results suggest that an increase in price would lead to a marked decrease in cigarette consumption in Canada.

(f) The interaction of cigarette smoking, as one risk factor in heart disease, and other risk factors such as cholesterol and blood pressure has been examined in a Canadian population (see K.S. Brown and W.F. Forbes, J. Gerontology, 30, 513-525, 1975). On the basis of these studies, the effects on life-span, depending on the levels of various risk factors,have been estimated. The effect of smoking on other diseases, including various cancers, has also been investigated (see, for example, J.F. Gentleman and W.F. Forbes, J. Gerontology, 29, 518-533, 1974).

(g) Cadmium, zinc and lead levels have been estimated in various tissues obtained at autopsy from smokers and non-smokers. At the same time, measurements have been made on connective tissue, in order to relate trace metal levels, as well as connective tissue status, to the probability of death from various degenerative diseases (see W.H. Cherry et al., Procs. 9th Ann. Conf. on Trace Metals in Environmental Health, University of Missouri-Columbia, 1975; W.H. Cherry and W.F. Forbes, J. Amer. Geriatrics Soc., 23, 14-21, 1975).

3. & 4. Statement of Significance of Project and Findings Relevant to Reducing Problems Associated with Non-Medical Use of Drugs

This project is intended to provide information useful in formulating policies directed towards reducing smoking in a Canadian population and developing a less hazardous cigarette. This goal is facilitated by making the relevant data available, and by suggesting means whereby these ends can be achieved.

5. Future Directions of Research Project

It is intended to continue the study as outlined in No. 2, since all these projects represent ongoing studies. Moreover, the work on carbon monoxide will be extended to include other gases as well. With respect to changes in tar and nicotine deliveries with time, it is intended to examine related changes which have taken place in other countries. With respect to the effects of advertising, it is intended to examine also the effect of advertising funds being spent on one particular cigarette, with a view to investigate whether a low tar and nicotine (a less harmful) cigarette would be more widely accepted if the appropriate advertising funds were increased. Also, another survey of Canadian school children is planned as soon as the necessary arrangements have been made.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
J.C. Hsia* J.C. Hsia	Pharmacology *

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Medical Sciences Building, University of Toronto, Toronto M5S 1A8

PROJECT TITLE – TITRE DU PROJET
Application of stable isotope labeling technique in the prevention of drug abuse - Compliance of methadone programs

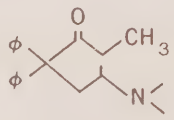
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975-76	$29,255.00	928-4084

FIELD OF RESEARCH – SUJET DE LA RECHERCHE: ☐ EVALUATION – ÉVALUATION ☐ BIOMEDICAL – BIOMEDICALE ☐ BEHAVIORAL – COMPORTEMENT ☐ SOCIAL SCIENCE – SCIENCES SOCIALES ☑ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

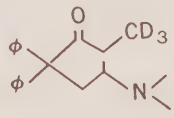
Methadone is widely used in well-organized treatment programs for heroin addiction. However, the effectiveness of these programs has been seriously hampered recently due to stringent controls imposed as a result of methadone abuse and diversion under the former, more lax dispensation of the drug. Dosages and take home privileges have been reduced, and many addicts have dropped out of the program or have not even bothered to enrol. The first objective of this research program is to develop an effective monitoring system for methadone treatment programs so that more liberal policies can again be implemented to effectively combat heroin addiction. One of the significant problems in the methadone treatment programs is that the therapist has no idea if the patient is taking his methadone as prescribed, or supplementing his dose with the same drug obtained illegally. No method of analysis currently exists that would allow this determination. The routine urine screening is only qualitative since the sample from a single voiding is analyzed without any clear notion as to what part of the 24 hour excretion of methadone and its metabolites it represents. The use of creatine or some other markers would not solve the problem since the excretion profile of these substances does not follow the urine production profile of methadone. However, if a deuterium labeled analogue of the drug which is indistinguishable metabolically from methadone can be prepared, the use of gas chromatography-mass spectroscopy (GC-MS) technique would provide a simple, sensitive, specific and reasonably inexpensive method for the detection of illicit supplementation.

The second objective of this research program is to determine the actual daily drug requirement of individual patients with the deuterium labeled methadone and GC-MS technique described above.

A number of deuterium labeled methadones (DEMON) have been synthesized. The following is one of these DEMONS.



Methadone



DEMON-3

By replacing the hydrogen atoms of c_1 with deuterium atoms, a trideuteriomethadone (DEMON-3) has been prepared and shown to have the same analgesic activity and toxicity in mice as methadone. The rate of absorption, distribution and excretion of DEMON-3 and methadone were identical in rats. These observations suggest that DEMON-3 may be used as an in vivo marker for monitoring compliance of methadone patients and thus may improve the effectiveness of methadone treatment programs.

DEMON-3 is currently being certified as a new drug by the Bureau of Drugs, Department of Health and Welfare. As soon as the drug is registered, limited human and clinical trials will be carried out at the Addiction Research Foundation of Ontario. If the preliminary trial proves to be satisfactory, large scale clinical trials will be carried out at methadone treatment centers across the country (Vancouver, Montreal and others).

Specific deuterium labeling of methadone and use of GC-MS technique permits rapid and quantitative determination of the ratio of labeled vs. unlabeled methadone in body fluids.

Clinical application of this technique could a) monitor cimpliance, b) detect diversion of methadone and c) determine the optimal drug requirement of each patient.

The deuterium labeling and GC-MS techniques can only be effectively employed by highly sophisticated scientists. The post-doctoral fellows employed in the present program can provide the expertise to implement this method at major methadone treatment centers, as in Vancouver.

Findings relevant to reducing problems associated with non-medical drug use are: a) the developed method would provide a means of control of abuse of methadone and increase the effectiveness of methadone treatment programs, b) it provides the first (novel) application of a well-established methodology (i.e. GC-MS) in improving the effectiveness of narcotic treatment programs, c) it may disprove the claim that methadone is an unmitigated menace to the community, since many people believe that the use of methadone in addiction treatment is followed, of necessity, by a flood of illicit methadone on the streets of their city, along with a high rate of methadone overdose deaths and primary methadone addiction.

If this project is successful, the basis will have been laid for future research in the improvement of other narcotic and psychoactive drug treatment programs.

*The co-applicants of this research program are Drs. A.E. LeBlanc and J.A. Marshman from the Addiction Research Foundation of Ontario. Dr. LeBlanc is also an Assistant Professor in the Department of Pharmacology, Faculty of Medicine, Dr. Marshman is an Associate Professor, Faculty of Pharmacy, University of Toronto.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
David P. Nowlis, Ph.D.	Institute of Community and Family Psychiatry
INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE	
Jewish General Hospital, Montreal, P.Q.	
PROJECT TITLE - TITRE DU PROJET	Training in voluntary self-governance for patients with self-governance effects on drug abuse

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1976-77	$24,225.00	514 341-6211

FIELD OF RESEARCH SUJET DE LA RECHERCHE	EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
	[ ]	[ ]	[ ]	[ ]	[X]

The first purpose of this study has been to study the relative effectiveness of biofeedback training, relaxation training, or a combination of both in promoting self-mastery in patients with self-governance disorders likely to lead to drug abuse. The second purpose has been to work toward more careful explication of the somatic and cognitive bases of individual concepts of "relaxation" in subjects with varying tendencies toward using drugs for treating psychosomatic disturbances arising from difficulties in achieving satisfactory states of relaxation.

Work toward the first goal has employed a rather large number of subjects randomly assigned to standardized training routines. Work toward the second goal has employed a small number of subjects given flexible training aimed at specified criteria of success in mastering voluntary self-governance of a wide variety of somatic processes related to relaxation.

On the first part of the project, 63 subjects were selected with relaxation related psychosomatic disorders, including insomnia, headache, and hypertension. All subjects used drugs in dealing with their symptoms, and all used more drugs than they wanted to take. A wide spectrum of drug use problems was present in the various subjects, including such things as repeated suicide attempts with drugs, addictions to prescribed drugs, "conning" of doctors to obtain desired drugs, refusals to abide by prescribed drug routines, dejection and loss of self-dignity at only being able to gain relief or control of the symptom through drug use, etc.

All subjects were given a medical history which included an extensive drug use interview, along with the Rotter I-E Scale,the Cattell 16 P.F. Test, and a family background questionnaire at the begining of the study. They were randomly assigned to three groups: biofeedback training, relaxation training, and control. All subjects kept home records on drug use and on symptomatology at monthly intervals during training or during the three-month-long control period. Urine samples were also collected at these times (the subjects were not told why).

After the three month control period, control subjects received a combination of biofeedback and relaxation training. Training periods in all cases included a minimum of 15 hour-long biweekly sessions, with most subjects opting for up to 20 sessions.

We have had far more volunteers and referrals for the project than we could possibly handle. Attrition in subjects accepted has been low (about 10%). Initial response to the program has been generally very enthusiastic on the part of the subjects, but it remains to be seen if the urinanalysis testing for drugs on all samples submitted will be as postive.

A follow-up study lasting for several sessions with each subject separately, including testing for continued ability in learned voluntary self-governance skills and further urine sampling, is planned for this summer.

Particular attention is being paid in our data analysis to trying to better define the dynamics of response to types of training. Our impression so far is that subjects with more severe drug abuse patterns show less predictable response to the training.

With respect to the second aim of the project, a small number of subjects are being trained in voluntary control of muscle tension, heart rate, skin temperature, skin resistance, EEG theta, EEG alpha, and EEG beta. These subjects then do a proximity analysis for us, comparing all poles of all processes which they have been able to master to preset criteria. The proximity data are then subjected to multidimensional scaling.

So far a solution has been achieved for only one subject on the latter problem. Three dimensions were apparent in his referent structure for somatic bases of relaxation, tentatively labeled as follows: "Flacidity" (low heart rate, low muscle tension), "deactivation" (high EEG theta, high skin resistance), and "involvement in the internal milieu" (high EEG alpha, high skin temperature).

We expect the latter project to help in better defining relaxation and in helping to eventually make training aims more specific and clear, and training considerably more efficient, at least training in relaxation potent enough to possibly reduce or eliminate unwanted consumption and strengthen self-governance systems to a point where drug abuse is less likely. Unfortunately, seven after mastery of relaxation and its somatic bases is successful, many important needs for self-growth may be left unmet, Better defining just what such training can and cannot do with various types of drug users should strengthen the possibility of meaningful liasons with other professions and other people interested in promoting the welfare of the person as a whole.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Ronald P. Schlegel	Kinesiology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
University of Waterloo, Waterloo, Ontario. N2L 3G1

PROJECT TITLE — TITRE DU PROJET
A social psychological study of non-medical drug use in secondary school and college students.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1974-77	$92,745.49	519-885-1211 Ext. 3089

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
[ ] EVALUATION — ÉVALUATION
[ ] BIOMEDICAL — BIOMEDICALE
[ ] BEHAVIORAL — COMPORTEMENT
[XX] SOCIAL SCIENCE — SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

The central concern of this study is the development of a general social psychological theory of drug use from which various primary and secondary prevention techniques may be derived. The relationship of variables both proximal (e.g., attitudinal, social expectancy) and distal (e.g., personality, perceived social environment) to drug use are investigated from a multivariate social learning perspective. Although marijuana use is examined in considerable detail, drug use patterns for tobacco, alcohol, amphetamines, barbiturates, heroin, hallucinogens, solvents and tranquilizers are also analyzed.

Approximately 2,000 high school students from two school systems (one urban, the other rural) have completed participating in a longitudinal survey consisting of five data points: the first four being four months apart and the fifth being 12 months after the fourth session. This design will permit sufficiently small time units to capture the more subtle changes in proximal variables as well as grosser time units of one and two years to permit analysis of changes in more distal variables. The longer time units should also permit the monitering of trends in consumption levels and patterns of multiple drug use. The longitudinal design of the survey study also provides for close attention to causal ordering (i.e., the order of attitude vs. behaviour change.)

Cross-sectional and longitudinal analyses focusing on the antecedent role of attitudes toward marijuana have lent strong support for the predictive validity of 20 attitudinal subscales. Cross-sectional multivariate analyses of the data collected at the first session also provided empirical support for the predictive validity of all variables systems in the study. However, the variance explained by proximal attitudinal and social expectancy variables was only marginally improved by the additional inclusion of distal personality and social environmental variables. More detailed cross-sectional and longitudinal analyses still remain to be completed. These analyses will include assessments of variables predicting "increasers" vs. "decreasers" of drug use. Factors predicting initiation and increased consumption levels would indicate the areas toward which primary and secondary prevention programs should be directed. Similarly, factors predicting decreased consumption levels should be suggestive of the processes upon which effective tertiary prevention or rehabilitative efforts may be based.

A more in-depth study of one particular personality variable has been investigated, namely, internal-external locus of control. Drug use has been related to each of its three dimensions -- fatalism, social systems control and self-control. Findings related to the latter dimension are particularly interesting in that persons lacking self-control use depressants more frequently and at the same time tend to avoid the use of stimulants and psychotomimetics. Clinical psychological methods for treating impulsiveness may have application to this situation.

Another study has assessed factors which differentiate controlled vs. uncontrolled alcohol drinking in adolescents. Proximal measures such as attitudes and normative beliefs, while being highly discriminative of nonuse vs. use in general, demonstrate a plateau effect when more advanced levels of alcohol consumption were being predicted. These variables, therefore, would not be viable content for reinforcement procedures designed to shape controlled drinking patterns. Future research will assess the ability of more distal personality and environmental factors in differentiating controlled vs. uncontrolled drinkers.

A major line of investigation has been to study the effects of persuasive communications on drug use attitudes, intentions and actual behaviour. It was found that certain attitudinal dimensions were more resistant to persuasive efforts, and others even prone to reactance effects. Some dimensions showed significant post-experimental impact, but this effect dissipated over time (6 weeks). Other dimensions were only slightly (i.e., nonsignificantly) affected by the immediate experiment, but continued to shift in the position advocated by the communication until a significant time effect was obtained over 6 weeks. Several reasons are postulated for these complex results. Another study is being conducted to partially discern some of these underlying processes. Considerable attention will be given by future research to explore the role of varying methods of persuasion (including role playing) in modifying attitudes and behaviour associated with patterns of non-medical drug use. Attitudes toward drug use appear to be complexly determined as well as being anchored to both personal and social experience. The difficulty of the problem will mandate a systematic sequence of investigation involving a number of studies, each respective one based on the findings preceding it.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Roy A. Wise	Psychology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Concordia University, Montreal

PROJECT TITLE — TITRE DU PROJET Noradrenergic, dopaminergic and serotonergic neural mechanisms and ethanol intake in the rat.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975-76	$15,000	514 879-4457

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
☐ EVALUATION — ÉVALUATION ☐ BIOMEDICAL — BIOMÉDICALE ☐ BEHAVIORAL — COMPORTEMENT ☐ SOCIAL SCIENCE — SCIENCES SOCIALES ☒ MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

Amit, Stern and Wise (Psychopharmacologia,1970,17,367-377) reported that lateral hypothalamic electrical stimulation caused elevated home cage intake of aversive (normally) ethanol solutions by rats. The present study was designed to determine if the elevated intake was causally related to the release of synaptic monoamines which is known to be caused by lateral hypothalamic stimulation. This information was hoped to shed light on the role of monoamine systems in normal voluntary intake of ethanol. The primary paradigm involved assessment of the effects of selective monoamine system lesions on the elevation of intake caused by stimulation.

Initial work was directed at learning and developing techniques for verification of neurochemically and anatomically specific monoamine lesions. The fluorescence histochemical methods of Falck and Hillarp and Battenberg and Bloom were learned and used in our lab to verify stereotaxic coordinates for catecholamine cell body and fiber locations. More recently variations on these methods were learned in Blooms lab for use in location of serotonin cell bodies and fibers. The assay method of Shellenberger and Gordon was also worked up in our lab. These techniques were used to verify lesions of the locus coeruleus, the substantia nigra and the A10 dopamine cell group as well as the fiber bundles of the dorsal tegmental noradrenergic bundle and the central tegmental noradrenergic tract.

Because bilateral lesions of catecholamine systems can cause sever aphagia, adipsia and sensory neglect, our design called for assessment of the effects of unilateral lesions. While unilateral lesions would not be expected to significantly alter spontaneous intake, they were expected to alter the elevation of intake which is caused by unilateral lateral hypothalamic stimulation. However, we were not able to see reliable changes in the effects of stimulation after locus coeruleus or substantia nigra lesions, and we no longer feel that this design can be fruitfully used. The major problem of this approach was that the elevation of ethanol intake caused by electrical stimulation is superimposed on a spontaneously increasing baseline intake level. Both the degree of change of baseline and the degree of increase due to stimulation have considerable variability, and the degree of variability from these two sources together obscures any systemmatic effects of the lesions. The ethanol intake in lesioned control animals was quite variable, and the intake in lesioned, stimulated animals was even more variable. Thus the unilaterally lesioned, unilaterally stimulated animal does not seem to be a fruitful preparation for assessing the role of monoamine systems in mediation of voluntary ethanol intake. The variability of ethanol intake in the unilaterally lesioned, unstimulated animals was sufficient to suggest that even this preparation would not be useful, and this consideration makes it obvious that the bilaterally lesioned, unstimulated animal would also be unsuitable for this type of study.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Roy A. Wise	Psychology

INSTITUTION AND ADDRESS ÉTABLISSEMENT ET ADRESSE
Concordia University, Montreal

PROJECT TITLE – TITRE DU PROJET
Neural mechanisms of brain self-stimulation and amphetamine self-administration

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-76		514 879-4457

FIELD OF RESEARCH SUJET DE LA RECHERCHE	EVALUATION ÉVALUATION	BIOMEDICAL BIOMEDICALE	BEHAVIORAL COMPORTEMENT	SOCIAL SCIENCE SCIENCES SOCIALES	MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE
					X

Our work focussed primarily on the roles of central noradrenergic (NA) and dopaminergic (DA) mechanisms in mediation of reward by intracranial stimulation and intravenous stimulant injection. Intracranial self-stimulation was disrupted by the NA blockers phentolamine and l-propranolol and by the DA blocker pimozide, regardless of whether the stimulating electrodes were in NA or DA systems. In each case it was unclear whether the reward value of stimulation or the response capacity of the animal was altered. Pimozide increased lever-pressing for intravenous stimulants when given at low doses; it caused increased responding that was followed by response cessation when given at high doses. These effects paralleled the effects of reward reduction and reward termination, respectively, and clearly did not reflect any drug-induced performance deficits. Phentolamine and l-propranolol decreased self-administration in a way that could not reflect drug-induced reward reduction (Yokel and Wise, Science 1975, 187, 547-549). These data suggested that the reward of intravenous stimulants stemmed from their known actions on DA systems, and was independent from their actions on NA systems. These suggestions were further supported by the finding that rats would self-administer the DA-specific receptor agonists apomorphine and ET 495, but not the noradrenergic agonist clonidine. Further, non-contingent injections of apomorphine and ET 495 caused pauses in self-administration, just as do non-contingent amphetamine injections; clonidine caused no such pauses.

The suppression of stimulant self-administration by l-propranolol was determined to be unrelated to NA receptor blockade, since d-propranolol, the inactive isomer had the same effect. The possibility that phentolamine failed to attenuate stimulant reward because the intraperitoneal injections given failed to cross the blood-brain barrier was ruled out by two findings. First, intraventricular injections of phentolamine at doses known to suppress self-stimulation did not attenuate amphetamine reward, as would have been reflected in increased amphetamine self-administration; rather they caused the same decrease in responding that was seen with intra peritoneal administration. Second, phenoxybenzamine, another receptor blocker of the alpha-NA type is known to readily cross the blood brain barrier and had no effect on amphetamine self-administration. In addition, blockade of NA synthesis with FLA-63 or U14-624 had no effect on amphetamine self-administration.

The reward-blocking effects of DA blockade with pimozide were confirmed with another DA blocker, [+]-butaclamol, whereas [-]-butaclamol, the inactive isomer had no effect.

The pattern of extinction responding seen under pimozide in the amphetamine self-administration paradigm suggested analysis of the temporal pattern of responding after pimozide in the self-stimulation paradigm. Temporal pattern of responding under conditions of high-dose pimozide (0.5mg/kg) and under conditions of non-reward were assessed in 10-sec time blocks. Responding was supranormal in both conditions for the first few minutes of testing, and then responding dropped out. In both conditions renewed normal responding was seen when access to the response lever was blocked and then reinstated. The bursts of normal responding at the begining of the session and after restricted access to the lever are well known aspects of operant behavior, termed "frustration responding" and "spontaneous recovery" respectively; these periods of responding indicate that high-dose pimozide does not attenuate self-stimulation by interfering with the ability to initiate voluntary movement or to organize complex motor acts. At lower doses of pimozide rates of responding for stimulation decreased as they do when stimulation current is reduced. Again the change in response rate followed a period of elevated "frustration" responding. Since pimozide was given 4h before testing, the gradual

decrease in response rates that accompanied both high and low doses of pimozide were not simply a consequence of pimozide absorption: pimozide reaches its maximum brain concentration and maximum effectiveness 4h after intraperitoneal injection. Thus as in the case of stimulant self-administration, pimozide administration alters self-stimulation by reducing the effective reward per response, rather than by reducing the response capacity of the animal (Fouriezos and Wise, Brain Res., in press).

In another line of study we examined the reported paradox that psychoactive drugs can be both rewarding and aversive. Stimulants, opiates and ethyl alcohol are self-administered by animals, and auditory and visual stimuli associated with injections of these agents acquire secondary (learned) reinforcing properties. Paradoxically, taste stimuli that are associated with similar injections of the same agents acquire aversive properties; thus the same drug can serve as an unconditioned stimulus for both learned reinforcement and learned aversion. We have ruled out the possibility that differences between the reward and aversion paradigms can account for the two effects. While factors like degree of drug familiarity, tolerance, dependence and expectation usually distinguish the two paradigms, we have found that both reward and aversion can be demonstrated in a paradigm where these factors are controlled. Animals can be used to demonstrate both reward and learned aversion from amphetamine in the same stage of their amphetamine treatment history. We also found that animals would lever-press for the very injections of apomorphine which caused aversion to associated saccharin. Thus it would appear that self-administered drugs do not represent simple rewarding stimuli. Rather they represent compound stimuli, and the compound can contain both rewarding and aversive elements(Wise, Yokel and deWit, Science, in press).

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
D G Frisk	Social and Preventive Medicine
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Manitoba	
PROJECT TITLE – TITRE DU PROJET	
Polypharmacy in Geriatrics	

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1974-76	$10,000.00	

FIELD OF RESEARCH – SUJET DE LA RECHERCHE

- ☐ EVALUATION – ÉVALUATION
- ☐ BIOMEDICAL – BIOMEDICALE
- ☐ BEHAVIORAL – COMPORTEMENT
- ☒ SOCIAL SCIENCE – SCIENCES SOCIALES
- ☐ MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

The drug (both prescription and "over-the-counter") taking and hoarding habits of a random sample of the population over the age of 65 (N-484) were obtained by interviews conducted by trained medical students. The interviews included both the interviewee's statement as to his/her habits and an inspection of those drugs on hand in the household.

It was found that the mean number of all drugs (prescription and O.T.C.) taken in the last three days was 2.66 and that there were statistically significant differences between males and females although there were no statistical differences in the various age groups or between social classes (as measured by occupation and education). The number of doctors with which an individual was in contact was significantly related to the number of those taken and hoarded, suggesting that those who were sick, or at least perceived themselves to be sick, were receiving and taking multiple medications. A detailed analysis of the results suggests that more than 80% of the over-65 population take three or less drugs per day and that few, if any of these carried with them hazards of over-medication or potentially dangerous drug interaction if taken as prescribed. Only about 10% of the sample fell into the category of heavy drug users (that is more than 5 drugs per day) and within this group was to be found those individuals on prescription medications from a number of doctors as well as taking "over-the-counter" drugs.

The findings of this study do not support the image of the elderly patient as being an inveterate drug taker and drug hoarder but it does suggest that proportion of the elderly which comes into contact with the Health Services needs to be monitored carefully with respect to the prescribing and management of their medications.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Lowell Gerson, Ph.D.	Department of Clinical Epidemiology and Biostatistics
INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE	
1200 Main Street West, Hamilton, Ontario	
PROJECT TITLE - TITRE DU PROJET	
Pilot Epidemiologic Field Station for Drug Related Problems	
YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES / TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE

FIELD OF RESEARCH — SUJET DE LA RECHERCHE

- ☐ EVALUATION — ÉVALUATION
- ☐ BIOMEDICAL — BIOMEDICALE
- ☐ BEHAVIORAL — COMPORTEMENT
- ☒ SOCIAL SCIENCE — SCIENCES SOCIALES
- ☐ MULTI-DISCIPLINARY — MULTI-DISCIPLINAIRE

The overall objectives of this project is to examine the feasibility of establishing Epidemiologic Field Stations for drug related problems and to evaluate the usefulness of such a unit as a prototype for a system of such units in Canada.

The station will be able to research and answer questions which are relevant in the development of strategies of prevention of drug related problems in both the local and national level. Examples of such programmatically relevant operations are:

I. What is the extent and distribution of various types and combinations of non-medical drug use and drug-related problems in the Canadian population, in geographic areas and over time?

II. What knowledge of personal and social characteristics (of individuals with various patterns of drug use or types of drug-related problems) is valuable to those responsible for treatment, rehabilitation and prevention services in Canada?

III. What is the course and outcome of drug-related problems of various types and severity? (i.e. what is the natural history of drug-related problems?).

IV. What are the social, behavioural and biological correlates of drug-related problems?

V. What are the factors and processes involved in person-to-person or place-to-place spread of drug-related problems, and in changes over time?

VI. What is the impact of institutional arrangements (e.g. legislative, criminal justice and supply systems) on drug-related problems?

VII. How can changes in the extent, distribution and pattern of drug-related problems be measured and assessed (directly and indirectly) and monitored early, reliably and efficiently and how should predictions be made?

VIII. What are the action implications of epidemiologic research for programmes of prevention, treatment and rehabilitation?

This project is particularly exciting as it is designed to develop a model for an innovative programme. While this unit will not be able to provide all the information necessary to answer questions regarding drug related problems, it is expected to:

1) integrate and coordinate various sources and types of data;

2) develop and improve methods and terminology;

3) produce better data for the development of more suitable epidemiologic methods;

4) contribute to the monitoring of changes in the nature, extent, distribution and inter-relations of drug-related problems;

5) provide a site for the training of personnel in appropriate epidemiologic concepts and methods;

6) and provide rapid feedback of information to the local community.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
P.J. Giffen	Sociology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
University of Toronto, Toronto

PROJECT TITLE – TITRE DU PROJET
Social Concomitants of Abstinence and Controlled Drinking in Skid Row Alcoholics

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
18 Months (August 1974-March 1976)	$46,602.34	595-6164

FIELD OF RESEARCH – SUJET DE LA RECHERCHE
[ ] EVALUATION – ÉVALUATION
[ ] BIOMEDICAL – BIOMEDICALE
[ ] BEHAVIORAL – COMPORTEMENT
[X] SOCIAL SCIENCE – SCIENCES SOCIALES
[ ] MULTI-DISCIPLINARY – MULTI-DISCIPLINAIRE

1. Description - Recent follow-up studies of alcoholic patients indicate that spontaneous remission and controlled drinking occur among a minority of alcoholics. The factors related to these phenomena have been suggested, but not systematically explored. Furthermore, few studies have examined the combination and pattern of treatment contacts that are related to maintenance of abstinence or controlled drinking.

In order to further examine these topics in a population with few social resources, a retrospective study was undertaken which involved interviews with 346 former and current male Skid Row inebriates. The sample consisted of available volunteers selected through regular field contacts with candidates and staff at 30 programs, institutions and caretaker centres with Skid Row clientele; by attending A.A. groups; and through regular contacts with Skid Row informants. In order to determine current or former Skid Row status, a screening interview was conducted focusing on main beverage consumed, drinking locale, type of accommodation, source of income, and number of arrests for public drunkenness in one year. Subjects who qualified were asked to participate in extended interviews which focused on changes in drinking patterns, history of recent illnesses, patterns in accommodation, sources of income, affiliations, family contacts, treatment contacts, demographic characteristics, and perceived circumstances or reasons for initiating or terminating periods of heavy consumption. One to two hour interviews were audio-recorded and selected areas were transcribed. Reliability data were collected from files at clinics, hospitals, detoxication units, etc. for 259 (75%) of the subjects.

2. Preliminary Results - Data analyses are still in progress; therefore, the factors related to recent drinking history have not been sufficiently isolated for analytical purposes.

Briefly, the majority of the subjects (76%) were between 35 and 59 years of age, almost all were born in Canada (90%), and almost two-thirds (60%) had fathers of Anglo-Saxon heritage. Most of the men (85%) claimed that the best jobs of their lifetime were of lower socio-economic status. The predominant current occupational statuses were: unemployed (27%), welfare (16%), steady work (16%), and pensions (14%). Almost all were either single (36%), separated (33%), or divorced (18%).

The study uncovered sufficient numbers whose drinking patterns had changed to make analysis possible. With regard to current drinking status, 9% had been abstainers for the past 12 months, 6% had been controlled drinkers over the past year, 11% had been partially controlled for the past year, 8% had been partially controlled in the past six months, 31% had not been drinking heavily in the past week and 35% had been drinking heavily in the past week. (A number of the currently active subjects had been abstinent at some point in the past few years.) Some of these categories were combined for analytical purposes.

The data tabulation has yielded information on the factors that the men perceive as being associated with diminished or increased drinking. (These subjective factors will be compared with objective changes in life-situations.) The subjects were asked how a person decided it was time to stop drinking or cut back on his drinking and the most frequent answers were extreme nausea and other aspects of withdrawal, for example "the shakes" (23%), dissatisfaction with one's physical and social conditions (21%), a serious illness (14%), and general concerns about health (13%). (The currently inactive drinkers were most likely to mention worrisome illness as a reason for stopping or controlling drinking.) The factors perceived as immediately preceding a period of abstinence or controlled drinking were extreme nausea or other aspects of withdrawal (18%), temporary lack of money (17%), a serious

illness (12%), a disgust with drinking and other aspects of lifestyle (11%), and obtaining a good job or other positive changes in circumstances (10%). The following factors were perceived as helping and maintaining controlled drinking or abstinence on a long-term basis: lack of funds (24%), finding means of keeping occupied or busy (21%), involvement in A.A. (16%), and association with non-drinkers (12%). Experiences that were considered to lead a person back to heavy drinking were: tragedies such as death or serious illness of relatives or friends (16%), problems in interpersonal relationships (14%), renewed affiliation with heavy drinkers (14%), and depression or discouragement about life-situation or lack of opportunities or resources (13%).

The analysis of objective factors in the mer's life situation is in the preliminary stage. Treatment variables are the first ones being considered. Some association has emerged between exposure to helping organizations and current drinking status. Although the currently inactive were most likely to have been in outpatient treatment a total of three months or longer, only one-third had undergone such treatment. Also, the currently inactive were most likely to have gone to A.A. regularly for several months; 50% had actually done so. However there was no significant relationship between current drinking status and total weeks in inpatient treatment programs. Sequential analyses are planned which will indicate the relationships between treatment contacts and subsequent drinking behaviour.

3. Significance of the Project - Previous studies have focused on the effects of particular treatment modalities on drinking behaviour. The present study examines the influence of other changes in life situation and of combinations and sequences of treatment experiences.

4. Relevance of the Findings for Reducing Problems - In view of the documented lack of success in most attempts to rehabilitate Skid Row alcoholics, new approaches are required. The present study should help in the planning of ameliorative measures intended to change the life situations of Skid Row alcoholics in ways likely to diminish their drinking and also in the focusing of intervention on the stages in their careers most amenable to change. The preliminary findings suggest, for example, that the onset of periods of abstinence or control are sufficiently often related to serious health problems that this may be one optimum time for initiating treatment contacts. Furthermore, the findings thus far suggest that the periods when they are most susceptible to treatment intervention are also times when they are also most favourably disposed to retraining programs intended to make them better able to handle employment situations, interpersonal relationships and leisure time, and that the maintenance of diminished drinking is dependent on the latter.

5. Future Directions of the Project - The intention is to monitor changes in both planned and unintended means of dealing with Skid Row alcoholics in order to test and expand the findings of the present study.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
N. Andrew Harrell	Sociology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
University of Alberta, Edmonton, Alberta

PROJECT TITLE — TITRE DU PROJET
Factors Affecting the Sentencing and Deterrence of Alcohol Related Offenses in Alberta

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975	$9000	7339490

FIELD OF RESEARCH — SUJET DE LA RECHERCHE
☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☒ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

This study examined differences in the sentencing of alcohol and non-alcohol related crimes in Edmonton between 1970 and 1974. The data used in this analysis were 1405 criminal cases drawn from probation files. Since our interest was in analyzing those offenses where there was a good likelihood that alcohol might be involved, only the following offenses were sampled: assault, disorderly behavior, homicide, armed robbery, rape, theft, vagrancy, vice, vandalism, drug offenses, drunkenness and petty theft. In examining the crosstabulation of alcohol use and categories of offense it was found that major crimes against the person made up the bulk of the sample. In addition, a high proportion (47.8%) involved the use of alcohol by the offender. For this reason, the present study focuses on the sentencing of major crimes against the person.

Among the findings, it was observed that for all offenses significantly more native persons than non-natives used alcohol while committing a crime. A significantly higher percentage of native persons than non-natives were involved in crimes against the person. In crimes against the person, significantly more natives used alcohol. Similarly, natives were more likely to use alcohol than non-natives while committing major property crimes.

A regression analysis of prison sentences for crimes against the person was performed using the following predictor variables: offender's sex, race, education and marital status; number of previous convictions; the offender's general attitude and remorsefulness, as judged by the probation officer; the probation officer's prognosis for the offender; the amount of personal injury suffered by the victim; the amount of monetary damage suffered by the victim. For crimes against the person involving alcohol in their commission, all of the predictor variables together accounted for 41.0% of the variation. The only significant predictors were race of the offender, offender's education and number of previous convictions. Natives received longer sentences than non-natives. Longer sentences were given to less educated and recidivistic offenders.

For crimes against the person not involving alcohol, only number of previous convictions and victim injury were significant, with longer sentences given to offenders with more previous convictions and where there was serious personal injury to the victim. Race of offender was negatively related to sentence with longer sentences going to non-natives.

Because of the strong association between race and sentence for crimes against the person where alcohol was involved, additional analyses were carried out to examine possible explanations for the relationship. One partial explanation for the association was that native persons received more severe sentences because they caused more personal injury when under the influence of alcohol. Another explanation explored was that native offenders had more extensive criminal records, particularly those involved in alcohol-related crimes. This proved not to be the case, however. Currently, research is being carried out examining the role of the victim in alcohol-related crimes involving natives. Preliminary evidence suggests that natives have a higher probability of being arrested for offenses involving alcohol use in private residences than in public places. In addition, the victim of crimes against the person committed by natives typically resides in this private residence and initiates the complaint against the offender. In the near future we hope to explore this relationship between the native offender and his victim in greater detail.

Regression analyses were also carried out for offenders who received probation rather than a prison sentence. Where alcohol was involved, the best predictor was the probation officer's

overall assessment of the offender's attitude. Offenders with good attitudes received shorter probationary terms than those with bad attitudes. Attitude was also the strongest predictor of length of probation in cases not involving alcohol, though this variable fell short of being statistically significant. The greater importance of the probation officer's subjective evaluations of the offender in cases where probation was given reflects a judge's inclination to pay more attention to what the probation officer has to say once the judge has decided that probation rather than a prison term is merited. When a judge has decided that prison is appropriate for an offender, less importance is placed on the probation officer's recommendations.

In addition to the variables which have already been mentioned, data are being collected on demographic variables and judicial attitudes towards sentencing associated with the sentencing judges in this study. The relationship between these characteristics of the judge and whether or not the judge makes use of different non-punitive, treatment-oriented sentencing options will be examined.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
John D. Hundleby	Psychology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Guelph, Guelph, Ontario N1G 2W1	
PROJECT TITLE – TITRE DU PROJET	
Individual and Environmental Predictors and Correlates of Adolescent Drug-Related Behaviour	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES
3	$82,825

TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE: 519-824-4120, Ext. 3562

FIELD OF RESEARCH SUJET DE LA RECHERCHE: ☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☒ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Project Description

The purpose of this study is to examine the extent to which variance in drug abuse behaviours among 9th grade adolescents may be accounted for by individual differences, environmental differences, and their interactions. Individual differences to be examined fell into three categories: Objective personality traits; self-report measures (social attitudes, behaviours and personality); and abilities. Environmental variables and dimensions come from: Home; family; friends; school (as a place); school (as a group of people); neighbourhood (as a place); and neighbourhood (as a group of people). The proposed research fell into three phases: first, the pretesting and developing of instruments to be used in the main study; second, conducting the main study on an Ontario-wide sample of 2,500 grade 9 students; and third, the analyses and write-up.

Pretesting: During the period from April 1974 to August 1975 our testing instruments were designed in the following manner. Initially the literature concerning drug use, the environment and other aspects of the study was examined and the major conceptual variables were extracted from each area of concern. From this examination questionnaires were designed which attempted to give maximal prediction of drug use behaviours and attitudes as well as to provide theoretical schemas to assist in the understanding of such predictors. These questionnaires were administered to approximately 1,200 grade eight and nine students in a total of nine southwestern Ontario schools. From these returns decisions concerning item addition, deletion and modification were made, largely on the basis of factor analyses of the various conceptual areas (e.g., the school as a place). Finally, two questionnaires were developed: a six-hour questionnaire for grade 9 students (N = 2,500) measuring the above individual and environmental differences and their relationships to drug use behaviours and attitudes; and a one-hour questionnaire for grade 10 students (N = 2,500) to be used for school environmental data and as an extension of our drug use epidemiological information.

Main Study

At the time of writing we are about 60% through the data collection and coding in the main study. The subjects for this phase were selected by first drawing schools on a stratified random basis (weighted by grade 9 enrollment) using Ontario region, system (Roman Catholic, separate, public) and size of schools as stratification factors. Students were then selected within each school on a random (though voluntary) basis.

2. Key Findings

The key findings to date come from the pretest data and involve the factor analyses of the various conceptual areas and the examination of the relationships of these factors to drug use and attitudes. These findings are presently being written up and should be available in two or three months.

3. Significance of the Study

The major significance of the study lies in its breadth: by taking such a broad sample of adolescents' attitudes, behaviours, personality characteristics, abilities and environmental differences, we will be able to make statements concerning the relative influence of these areas and variables on drug use and attitudes. Also we can view drug usage as a behaviour among a wide range of other behaviours and attitudes such as delinquency, dating, social activities, school achievement, athletic activities and so on. Further, the study will provide adolescent drug use epidemiology data on the entire province of Ontario, including areas which have previously received little examination such as the far north. Finally, we hope to place our empirical results in a broad theoretical framework concerning adolescent drug usage.

4. Relevance to Reducing Problems Associated with Non-Medical Drug Use

This is a study of the etiology of adolescent drug usage. As such its main thrust in this area will be in terms of prevention. It is hoped that the result will indicate those areas, particularly environmental, where preventive attention may be most usefully focused.

5. Future Directions

Based on our empirical findings certain areas (perhaps environmental, personal, or interactive) should appear as maximally important. Future research would be along these lines.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
S.W. Sadava	Psychology

INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE
Brock University, St. Catharines, Ontario.

PROJECT TITLE – TITRE DU PROJET
Longitudinal Social Learning Study of Non-Medical Drug Use in Adult Working Samples

YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED – SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER – NUMÉRO DE TÉLÉPHONE
1975/76	$19,250.00	416-684-7201 Ext. 445

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMÉDICALE [X] BEHAVIORAL COMPORTEMENT [X] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

Funding was for two purposes:
1. to conduct further multivariate analyses in writing up data from an earlier longitudinal study.
2. to conduct the preliminary research for an extensive longitudinal study in working populations.

With regard to the former, a repeated-measures study had been conducted over one academic year of cannabis and other drug use among students. Personal and social variables, and changes in these variables were shown to be predictive of changes in status as a user or non-user of illicit drugs, and of the patterns of use of these drugs. The problems of defining and measuring criterion measures of drug use (and "abuse") and of identifying the sets of personal and social predictions (including person-environment interaction components) were shown to be crucial and difficult, but not intractable. The use of multivariate techniques of analyses proved particularly useful here. The following reports are available:

1. Sadava & Forsyth. Turning on, turning off and relapse: social psychological determinants of status changes in cannabis use. In press, International Journal of the Addictions.
2. Sadava & Forsyth: Person-environment interaction and college student drug use: a multivariate longitudinal study. In press, Genetic Psychology Monographs.
3. Sadava & Forsyth. Decisions about drug use: an application of the choice-shifts paradigm. In press, Psychological Reports.
4. Forsyth & Sadava. Criteria measures of drug-using behavior: multivariate analyses. Submitted. With regard to the latter purpose, a questionnaire was designed and pre-tested, containing measures of:
   1. Predispositional personality - disjunctions among goals, values and expectancies, values for risk, reduced personal controls (time perspective, religiosity).
   2. Predispositional environment - perceived job and life-change stress, demography.
   3. Personal positive and negative functions for alcohol and cannabis use.
   4. Perceived alcohol related and drug-related environment such as social support, absence of sanctions, availability of alcohol and drugs.
   5. Multiple measures of alcohol, cannabis and polydrug-using behaviour.

At present data is being collected from samples of factory workers, nurses and teachers. Sample sizes will be adequate for the purposes of measurement assessment, preliminary hypothesis testing, and as bases for longitudinal study.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER – NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT – DÉPARTEMENT
Mark L. Sandilands	Department of Psychology
INSTITUTION AND ADDRESS – ÉTABLISSEMENT ET ADRESSE	
University of Lethbridge, Lethbridge, Alberta, Canada T1K 3M4	
PROJECT TITLE – TITRE DU PROJET	
Dimensions of Drug Abuse	
YEARS FUNDED – ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED SUBVENTIONS ASSIGNÉES
1974, 1975-76	$8745.00

TELEPHONE NUMBER
NUMÉRO DE TÉLÉPHONE
329-2404

FIELD OF RESEARCH SUJET DE LA RECHERCHE

- [ ] EVALUATION ÉVALUATION
- [ ] BIOMEDICAL BIOMEDICALE
- [ ] BEHAVIORAL COMPORTEMENT
- [X] SOCIAL SCIENCE SCIENCES SOCIALES
- [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

The purpose of this study was to investigate the perceptions of and thus the attitudes towards 17 common non-medically used drugs. Three groups were investigated: drug users, professionals involved in treating or otherwise dealing with drug users, and police. One goal was to determine the ways in which these three groups view drugs; the second goal was to compare the separate views of the three groups. It was suspected that since each group has a different mode of contact with drugs, they would have different views of the drug domains. The approach used was multidimensional scaling (MDS) analysis of the dissimilarity judgements of all possible pair combinations of the 17 drugs. Results indicated that each group's view of drugs was based on two dimensions. Although the three sets of views were similar, they were sufficiently different to warrant separate labels. These differences were noted particularly in contrasting sets of drugs, i.e., which set of drugs was seen to be most different from, for example, the opiates. With respect to similarity, the users were most different from police, with professionals in-between these two groups.

In applying this study to problems associated with non-medical drug use, with some further work the results can be incorporated into the training of law enforcers and professionals by showing these groups how drugs are perceived by users and increasing the credibility and acceptability of these groups among users.

The further work would involve, for example, examinations of differential similarity to user perceptions among high success and low success professionals.

Paper presentation resulting from project:

Three separate worlds: Perceptions of drugs held by drug users, drug professionals and police. Read at 10th Annual Conference of the Canadian Foundation on Alcoholism and Drug Dependencies. Quebec City, September 1975.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
E.M. Sellers, Ph.D.	Departments of Medicine and Pharmacology

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
Clinical Institute, Addiction Research Foundation, University of Toronto, Tor. Ont.

PROJECT TITLE TITRE DU PROJET Epidemiology, Treatment and Analytical Services in Adult Drug Overdose in Metropolitan Toronto.

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE

FIELD OF RESEARCH SUJET DE LA RECHERCHE
☐ EVALUATION ÉVALUATION ☐ BIOMEDICAL BIOMEDICALE ☐ BEHAVIORAL COMPORTEMENT ☒ SOCIAL SCIENCE SCIENCES SOCIALES ☐ MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

TACTICS FOR STUDIES OF ADULT DRUG ABUSE: A 2 year project has been initiated to determine: 1) changing patterns and patient characteristics associated with adult drug abuse in Toronto, Canada; 2) the role of quantitative and qualitative drug analysis in the clinical mangement of "overdose" patients; 3) to identify "high risk" patients towards whom specific therapy and preventive measures can be directed. Nurses record demographic and clinical features of patients abusing drugs presenting to the 21 acute care hospitals in metropolitan Toronto. At the Clincial Institute and Toronto Western Hospital, detailed in-patients management isalso monitored and serial blood concentrations related to clinical status. Initial results (3 months, 148 patients) from these 2 hospitals indicate the most common "alleged" suicidal drugs are: alcohol (41%), benzodiazepines (32%), barbiturates (17%) and salicylates (12%). Alcohol was confirmed to be present in 25%. Multiple drug ingestion occurs in 40% of patients. Only 26% of overdose patients required admission to hospital. Chronic drug abuse patients (243) report using tetrahydro-cannabinol derivatives (17.1%), "speed" (11.6%), benzodiazepines (7.8%), barbiturates (8.0%). Drug analysis was requested by physicians in 35 percent of overdose and drug abuse patients. None of the alleged drugs were present in 39% of patients and all alleged drugs were present in 20%. Cumulating data indicate patterns of drug abuse across the city are similar despite socio-economic differences. Patient history is unreliable to identify drugs after acute ingestion but serum concentration measurement is not clinically indicated in the majority of cases. (Supported in part by the Non-Medical Use of Drugs Directorate.)

DRUG ANALYSIS IN MANAGEMENT OF DRUG OVERDOSE: Detailed surveillance of drug overdose patients presenting to the emergency departments of 21 acute care Toronto hospitals is being carried out to determine: 1) patient characteristics; 2) regional variations in overdosage patterns; 3) variations in acute management; and 4) the usefulness of quantitative and qualitative drug analysis in clinical management. A majority of overdose patients (approx. 70%) in all hospitals had toxicologic drug analysis ordered by the treating physician. Blood, urine and gastric drug analysis constituted 73%, 24% and 2.6% respectively of 7958 requests (6 months). Yield on serum analysis is low and this pattern of sample submission is inefficient. Only 25% of samples analyzed were positive for any drug and only 10% contain all drugs allegedly taken. Patient history is unreliable. In 190 patients allegedly ingesting only ethanol, barbiturates 24%, salicylates 9%, nonbarbiturate sedatives 8%, bromides 5%, nonsalicylate analgesics 4%, phenothiazines 4%, antidepressants 3%, solvents 3%, narcotics 1%, were found. Despite the inaccuracy of history there is no evidence to date that costly toxicologic analysis is efficiently requested or that it contributes significantly to decrease morbidity and mortality in overdose patients.

CONCURRENT ALCOHOL USE IN DRUG OVERDOSE: Prospective surveillance of approximately 4250 acute drug ingestion and drug abuse patients in 21 hospital emergencies in Metropolitan Toronto between October 1, 1974, and September 30, 1975, indicates that alcohol is frequently reported as a concurrently ingestion drug. Data analysis is completed up to March 30, 1975 and indicates 547 (31.3%) of 1746 patients reported alcohol consumption immediately prior to the emergency room visit. Blood alcohol was actually determined in 451 patients. Alcohol was confirmed to be present in 74.7% of 198 patients alleging to take alcohol. In patients who do not claim to have ingested alcohol only 1% are found to have alcohol in their blood. A detailed interview of 67 admitted overdose patients in 2 teaching hospitals indicated higher than average Canadian alcohol intake. The mean ethanol consumption of the group was 43 g per day. Forty-three subjects ingested 20 grams alcohol per day ($p < 0.01$). In this group of subjects, benzodiazepines were more commonly ingested ($p < 0.05$) and salicylates less commonly ingested ($p < 0.01$) than by individuals consuming less than 20 g per day. Patients with a history of alcohol ingestion 20 g per day prior to admission had a higher rate of previous drug overdose ($p < 0.02$) and were typically unemployed, had more arrests, were more transient and has a higher incidence of family alcoholism. These preliminary results indicate that alcohol is more frequently taken as part of a suicide attempt by individuals with a history of heavier alcohol use and that there are differences in other patterns of drug abuse by this group. A patient's statement to have taken alcohol as part of an acute drug overdose usually indicates that alcohol will be found on blood analysis hence the usefulness of doing the test is limited. The prominence and potential importance of alcoholism in acute drug overdose needs clarification.

Health and Welfare Canada Santé et Bien-être social Canada

NAME AND SIGNATURE OF RESEARCHER — NOM ET SIGNATURE DU CHERCHEUR	DEPARTMENT — DÉPARTEMENT
Gerald Walker	Geography

INSTITUTION AND ADDRESS — ÉTABLISSEMENT ET ADRESSE
York University, 4700 Keele St., Downsview, Ontario

PROJECT TITLE — TITRE DU PROJET
Heroin Addiction, Methadone Maintenance and Geographic Space

YEARS FUNDED — ANNÉES SUBVENTIONNÉES	FUNDS ALLOCATED — SUBVENTIONS ASSIGNÉES	TELEPHONE NUMBER — NUMÉRO DE TÉLÉPHONE
1975-76	$29,500	667-6272

FIELD OF RESEARCH SUJET DE LA RECHERCHE: [ ] EVALUATION ÉVALUATION [ ] BIOMEDICAL BIOMEDICALE [ ] BEHAVIORAL COMPORTEMENT [X] SOCIAL SCIENCE SCIENCES SOCIALES [ ] MULTI-DISCIPLINARY MULTI-DISCIPLINAIRE

1. Description:

Intensive interviews were conducted with 105 current methadone users. The interviews provided socio-economic profiles, behavioural characteristics and interaction data at three periods in the interviewees life: at time of heroin addiciton, at time of first legal methadone use and at present.

Analysis is directed toward establishing relationships between these three clusters of variables over the period of methadone maintenance. Secondly it is hoped to use interaction data as a basis for simulations of the spread of methadone among the population of susceptable heroin users.

2. Key findings:

Analysis is in a preliminary stage and findings are almost entirely descriptive. Further, they must be treated as extremely tentative.

1) While methadone users come from the entire range of socio-economic status positions, the social centre of gravity is in the working class.
2) There is some indication that heroin use is associated with unsuccessful coping efforts at the interface between the poverty and respectable working class strata of the populations.
3) Throughout heroin use and into methadone maintenance users maintain social ties with friends and relatives
4) The spread of methadone use follows a boundedly random spatial pattern which is similar to other diffusions of innovations studied by geographers.
5) Other than broad spectrum characteristics at the social level, users of heroin and methadone are primarily marked by social network links to prior users.

3. Significance of Project:

The methadone users study has assembled the only substantial data set which combines social and geographic information about users, over several crucial life cycle positions.

4. Findings Relevant to Reducing Problems Associated with Non-Medical Drug Use:

It is premature to identify such findings.

5. Future Directions of the Research Project:

Primarily in the direction of detailed examination of social network structures and their changes over time.

APPENDIX

Names of all Principal Investigators and their project titles

APPENDICE

Nom des chercheurs principaux et les titres de leurs projets

NEWFOUNDLAND
TERRE-NEUVE

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
REVUSKY, S.	Basic Research Relevant to the Chemical Aversion Treatment of Alcoholism 1975

NOVA SCOTIA
NOUVELLE-ÉCOSSE

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ECOBICHON, D.J.	The Placental and Milk Transfer of Chronic Low Doses of Methadone, its Pharmacokinetics and Effects on Morphological and Biochemical Aspects of Hepatic Function in the Neonatal Guinea Pig
RUOTOLO, R.	The Atlantic Region Research and Development Team for Drug Treatment Programs

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PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
AMIT, Z.	Aversion and Reinforcing Mechanisms of Drug Dependence
BELLEAU, B.	In Vivo N - Dealkylation of Opiates in Relation to Agonist - Antagonist Actions
BIRMINGHAM, M.K.	Effects of Δ^9-THC on Mitochondrial Respiration
CAILLÉ, G.	Création d'un centre de détection et de dépistage des drogues
HOSEIN, E.A.	A Subcellular Model From Brain Which Likely Reflects Changes Taking Place in the CNS of Rats Subsequent to Administration of Opiates and Their Antagonists
	Hepatotoxicity of Ethanol in Rats, Following Chronic Administration
KRNJEVIC, K.	Action of Morphine on Neurones and Synaptic Transmission in Brain and Spinal Cord
LAMONTAGNE, Y.	Étude comparée de l'arrêt des pensées, du contrat behavioral et de la combinaison des deux techniques sur le comportement des fumeurs
	Rôle de la rétroaction biologique (Biofeedback) par EEG et EMG dans la prévention de l'abus des drogues
MILSTEIN, S.L.	Traitement de l'abus des drogues: recherche et développement
MURPHY, H.B.M.	Hidden Barriers to the Diagnosis and Treatment of Alcoholism

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PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
NOSAL, G.	Consequences of Maternal Narcotic Dependence of the Infant Animal. Short-Term Effects
NOWLIS, D.P.	Training in Voluntary Self-Governance for Patients with Self-Governance Effects on Drug Abuse
PIHL, R.O.	Extra-Pharmacological Factors in Drug Intoxication
RANGNO, R.E.	Non-Medical Use of Drugs in Suicidal Overdose: Research into Some Problems
WISE, R.A.	Neural Mechanisms of Brain Self-Stimulation and Amphetamine Self-Administration
	Noradrenergic, Dopaminergic and Serotonergic Neural Mechanisms and Ethanol Intake in the Rat

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
BASRUR, P.K.	Studies Related to the Test Systems and Biological Activities of Cigarette Smoke
BOEGMAN, R.J.	Brain Gangliosides in Drug Addictions
BROWN, I.R.	Effect of Psychotropic Drugs on Gene Activity in Neural Tissue
FENZ, W.D.	Psychophysiological Reactions to Cannabis Sativa in Chronic Users
FORBES, W.F.	The Waterloo Smoking and Health Project
GERSON, L.	Pilot Epidemiologic Field Station for Drug-Related Problems
GIFFEN, P.J.	Social Concomitants of Abstinence and Controlled Drinking in Skid Row Alcoholics
GILBERT, R.M.	Temporal and Volitional Factors in the Development and Assessment of Physical Dependence on Ethanol in Rats
GOLDSTEIN, S.	Cultured Human Fibroblasts: An In Vitro System to Detect Toxic Effects of Delta 9 THC
HIRST, M.	Studies into Behavioural, Neurochemical and Treatment Aspects of Heroin and Ethanol Intoxications
HSIA, J.C.	Application of Stable - Isotope Labelling Technique in the Prevention of Drug Abuse - Compliance of Methadone Programs

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
HUNDLEBY, J.D.	Individual and Environmental Predictors and Correlates of Adolescent Drug-Related Behaviour
JONEJA, M.G.	Teratogenic and Cytogenic Effects of Marijuana and Δ^9-THC in Rodents
KRISTOFFERSON, A.B.	Changes in Human Time Perception due to Delta 9 THC
LAVERTY, S.G.	Treatment Programme Development Research in Frontenac County
MACCONAILL, M.	Mechanisms of Adverse Reactions to Psychotropic Drugs: I. MDA
MACLEAN, A.W.	Responding During Sleep: A Paradigm for Drug Evaluation
MAYERSOHN, M.	The Disposition and Response Kinetics of Disulfiram in Dogs
MAZURKIEWICZ-KWILECKI, I.M.	Pharmacological Studies on Mandrax and Methaqualone
PAPPAS, B.	An Exploratory Investigation of Pavlovian Mechanisms in Morphine Tolerance
PETERS, D.A.V.	Analytical Service Facility - Identification of Psychotropic Agents in Untowards Reactions
SADAVA, S.	A Longitudinal Social Learning Study of Non-Medical Drug Use in Adult Working Samples
SELLERS, E.M.	Epidemiology, Treatment and Analytical Services in Adult Drug Overdose in Metropolitan Toronto

ONTARIO

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
SCHLEGEL, R.P.	A Social Psychological Study of Non-Medical Drug Use in Secondary School and College Students
SMITH, C.T.	The Relation Between Paradoxical Sleep and Drug Addiction
SMITH, J.A.	Synthesis of Radiolabelled Tetrahydrocannabinol Derivatives
STRETCH, R.	Experimental Investigations of Behavioural and Pharmacological Determinants of Drug Dependence in Monkeys
TONG, J.E.	Effects of Ethanol and Tobacco on Human Performance and Physiological Variables
TRITES, R.	Neuropsychological and Psychosocial Antecedents and Chronic Effects of Prolonged Use of Solvent and Methamphetamine
VOGEL-SPROTT, M.D.	Social Drinkers: Self-titration Training Effects on Attitudes and Use of Alcohol; Factors Determining Behavioural Effects of Alcohol
WALKER, G.	Heroin Addiction, Methadone Maintenance and Geographic Space
WOOD, G.W.	Application of Field Disorption Mass Spectrometry to Rapid Identification of Drugs of Abuse

MANITOBA

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
FISH, D.G.	Polypharmacy in Geriatrics
HAVLICEK, V.	Abnormalities of Brain Electrical Maturation of Sleep States in Newborn Infants of Chronic Alcoholic Mothers
REID, A.E.	Knowledge and Social Action: A Study of the Impact of Research on Alcohol and Drug Treatment

SASKATCHEWAN

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
BOULTON, A.A.	Identification and Quantitative Analysis of Amphetamine and Some of its Metabolites and Their Effect on Certain Trace Amines
	Identification and Quantitative Analysis of Certain Condensation Substances formed from Alcohol and Aryl Alkyl Amine Metabolites
HINDMARSH, K.W.	Development of Rapid Forensic Procedures for the Analysis of Selected Drugs
JOHNSON, G.E.	The Influence of Chronic Ethanol Consumption on Drug Absorption, Distribution and Elimination
WENGER, B.S.	Drugs and Behavioural Teratogenesis
YARBROUGH, G.C.	Narcotic Interactions with CNS Biogenic Amines at the Synaptic and Neuronal Level

ALBERTA

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ADAM, F.C.	New Methods in Immunoassays Using Fluorescent Labels
CLARK, S.C.	Clinical Assessment of Opiate-Like Drugs and Their Antagonists in Man
HARRELL, W.A.	Factors Affecting the Sentencing and Deterrence of Alcohol - Related Offences in Alberta
KNAUS, E.E.	New Analytical Techniques for the Separation, Identification and Quantitation of Cannabinoids and Their Metabolites
SANDILANDS, M.L.	Dimensions of Drug Abuse
ZELHART, P.F.	Non-Medical Use of Drugs Treatment Program Development Research: Alberta and District MacKenzie, Northwest Territories

BRITISH COLUMBIA
COLOMBIE-BRITANNIQUE

PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
ALEXANDER, B.K.	Evaluation of a Programme of Family Therapy for Heroin Addiction
BELLWARD, G.D.	Effect of Methadone, Dieldrin and Other Drugs on Rat Hepatic Microsomal Epoxide Hydrase and Aryl Hydrocarbon Hydroxylase
BEST, J.A.	Smoking Withdrawal Procedures Tailored to Individual Reasons for Smoking
CAMPBELL, D.J.	Hospital-Based Reference Drug Abuse Analytical Laboratory
FIBIGER, H.C.	Neurochemical Substrates of Drug-Reinforced Behaviour
MCGEER, P.L.	Possible Structural and Biochemical Alterations in the Brain Tissue Following Δ^9-THC Administration
PINEL, J.P.J.	Development of Alcoholism Treatment Programs in British Columbia: Biomedical Treatment Modalities
	Repeated Administration of Convulsive Agents and the Alcohol Withdrawal Syndrome
QUASTEL, J.H.	Effects of Psychotropic Drugs on Transmitter Formation and Release in Brain
SANDERS, H.D.	The Effects of Delta - 9 - THC on the Respiratory Mechanics of Asthmatic Patients

BRITISH COLUMBIA
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PRINCIPAL INVESTIGATOR CHERCHEUR PRINCIPAL	TITLE OF PROJECT TITRE DU PROJET
STORM, T.	Observational Study of Alcohol Consumption in Natural Settings
WADA, J.A.	Preclinical Evaluation of the Anti-epileptic Properties of Cannabis Sativa